

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
28 June 2001 (28.06.2001)

PCT

(10) International Publication Number  
**WO 01/46178 A2**

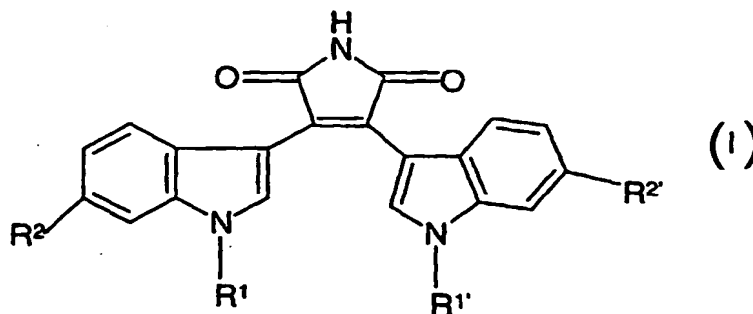
- (51) International Patent Classification<sup>7</sup>: C07D 409/00
- (21) International Application Number: PCT/EP00/13026
- (22) International Filing Date:  
21 December 2000 (21.12.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/171,557 22 December 1999 (22.12.1999) US
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- (81) Designated States (*national*): AE, AL, AM, AT, AU, AZ,  
BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE,  
ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,  
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,  
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,  
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ,  
VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— Without international search report and to be republished  
upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED PYRROLES

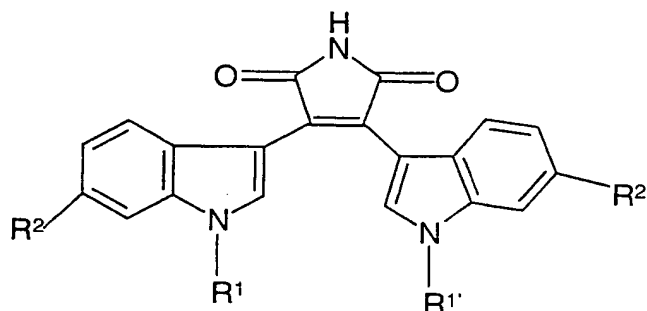


(57) Abstract: Disclosed are substituted pyrroles having formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>1'</sup> and R<sup>2'</sup> are as defined in the claims and in the description. These compounds and their pharmaceutically acceptable salts are useful in the treatment and/or control of cell proliferative disorders, in particular cancer. Also disclosed are pharmaceutical compositions containing the foregoing compounds.

5

### Substituted Pyrroles

10 The invention relates to substituted pyrroles. More particularly, the invention relates to substituted pyrroles of the formula



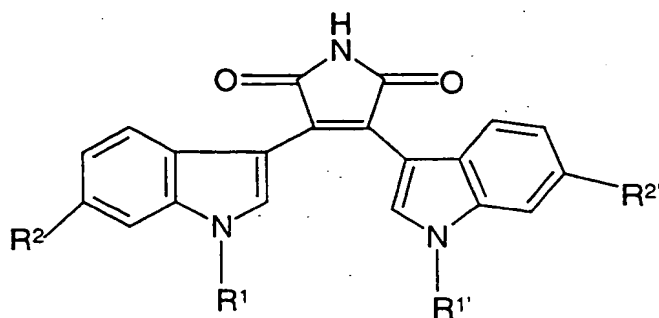
wherein

- 15  $R^1$  and  $R^{1'}$  are independently hydrogen, lower alkyl, lower alkenyl or lower alkynyl;
- $R^2$  is hydrogen, nitro, cyano, halogen, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy; and
- 20  $R^{2'}$  is a heteroaryl, heterocycle, ethyl substituted with a heteroaryl, or ethoxy substituted with a heteroaryl or heterocycle; or
- a pharmaceutically acceptable salt thereof.

The compounds of the invention are useful in the treatment or control of cell proliferative disorders, in particular cancer, particularly the treatment or control of solid tumors. In particular, the compounds of the invention have antiproliferative activity, specifically, they inhibit cell division in G2/M phase of the cell cycle.

### Detailed Description of the Invention

30 The invention relates to substituted pyrroles. More particularly, the invention relates to substituted pyrroles of the formula



wherein

$R^1$  and  $R^{1'}$  are independently hydrogen, lower alkyl, lower alkenyl or lower alkynyl;

$R^2$  is hydrogen, nitro, cyano, halogen, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy; and

$R^{2'}$  is a heteroaryl, heterocycle, ethyl substituted with a heteroaryl, or ethoxy substituted with a heteroaryl or heterocycle; or

a pharmaceutically acceptable salt thereof.

As used herein, the term “**lower alkyl**”, alone or in combination, means a straight or branched chain alkyl group containing a maximum of 3 carbon atoms, such as methyl, ethyl, propyl, and isopropyl, which is unsubstituted or substituted by one or more of hydroxy, lower alkoxy, amino, halogen, thio-lower alkyl or lower alkylsulphanyl. Examples of lower alkyl substituted by one or more halogen includes chloromethyl and trifluoromethyl.

The term “**lower alkoxy**”, alone or in combination, means a group wherein the lower alkyl residue is defined as above, for example, methoxy, ethoxy, propoxy, isopropoxy and the like.

The term “**heteroaryl**”, alone or in combination, means a 5 or 6 membered aromatic ring containing 1 to 4 heteroatoms which may be the same or different, and where the ring is unsubstituted or substituted by one or more of halogen, lower alkyl, hydroxy, carboxy, lower alkoxy, nitro, amino or cyano. The heteroatom(s) are selected from the group consisting of nitrogen, sulfur and oxygen. Examples of heteroaryl are furan, thiophene,

5 pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, oxadiazole, triazole, tetrazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, and triazine.

The term “**heterocycle**”, alone or in combination, means a 4 to 7 membered non-aromatic ring containing one or more heteroatoms which may be the same or different, and  
10 where the ring is partially or completely saturated and where the ring is unsubstituted or substituted by one or more of halogen, lower alkyl, hydroxy, carboxy, lower alkoxy, nitro, amino or cyano. The heteroatom(s) are selected from the group consisting of nitrogen, sulfur and oxygen. Examples of unsubstituted heterocycle are pyrroline, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, pyran, piperidine, dioxane,  
15 morpholine, dithiane, thiomorpholine, piperazine, and trithiane.

The term “**halogen**” means fluorine, chlorine, bromine or iodine.

The term “**amino**” means an unsubstituted amine group or an amine substituted by  
20 one or more substituents selected from alkyl, aryl, acyl, alkylsulfonyl or arylsulfonyl,

The term “**alkenyl**” means a straight or branched chain hydrocarbon group of 2 to 5 carbon atoms having at least one double bond.

25 The term “**alkynyl**” means a straight or branched chain hydrocarbon group of 2 to 5 carbon atoms having at least one triple bond.

In formula I above, preferably,  $R^1$  and  $R^{1'}$  are independently hydrogen, methyl or ethyl, which are unsubstituted or substituted by lower alkoxy, preferably methoxy or ethoxy.  
30 Most preferably, at least one of  $R^1$  and  $R^{1'}$  is lower alkyl, most preferably unsubstituted methyl.

Preferably, when  $R^2$  is lower alkoxy, it is methoxy or ethoxy, most preferably methoxy. Preferably, when  $R^2$  is lower alkyl, it is methyl or ethyl, which is unsubstituted or  
35 substituted by one or more of lower alkoxy or halogen. Most preferred when  $R^2$  is lower

- 5 alkyl it is methyl, which is unsubstituted or substituted by methoxy.  $R^2$  may also preferably be haloalkyl such as trifluoromethyl.

When  $R^{2'}$  is heteroaryl, it is preferably thiophenyl, furanyl, imidazolyl which is unsubstituted or substituted with lower alkyl, thiazolyl, pyrazolyl which is unsubstituted or  
10 substituted with lower alkyl, pyrimidinyl, or isothiazolyl.

When  $R^{2'}$  is heterocycle, it is preferably unsubstituted morpholine, unsubstituted pyrrolidine, unsubstituted piperidine, or piperazine which is unsubstituted or substituted  
15 with lower alkyl, lower alkoxy or carboxy.

When  $R^{2'}$  is ethyl substituted with heteroaryl, preferably the heteroaryl is imidazole. In addition,  $R^{2'}$  may be methyl or propyl substituted with a heteroaryl.

In addition to ethoxy substituted with a heteroaryl or heterocycle,  $R^{2'}$  may also be  
20 methoxy or propoxy substituted with a heteroaryl or heterocycle.

In a preferred embodiment, when  $R^{2'}$  is thiophenyl, preferably  $R^1$  and  $R^{1'}$  are both methyl and  $R^2$  is hydrogen or nitro.

25 In another preferred embodiment, when  $R^{2'}$  is furanyl, preferably  $R^1$  is hydrogen, methyl,  $R^{1'}$  is methyl, and  $R^2$  is hydrogen or nitro.

In another preferred embodiment, when  $R^{2'}$  is imidazolyl which is unsubstituted or substituted with lower alkyl, preferably, methyl, preferably  $R^1$  is methyl  $R^{1'}$  is methyl and  
30  $R^2$  is hydrogen, nitro, cyano, halogen or methoxy.

In another preferred embodiment, when  $R^{2'}$  is thiazolyl, preferably  $R^1$  and  $R^{1'}$  are both methyl and  $R^2$  is hydrogen or nitro.

5           In another preferred embodiment, when  $R^{2'}$  is pyrazolyl which is unsubstituted or substituted with lower alkyl, preferably methyl, preferably  $R^1$  and  $R^{1'}$  are both methyl and  $R^2$  is hydrogen, nitro or halogen.

10           In another preferred embodiment, when  $R^{2'}$  is pyrimidinyl, preferably  $R^1$  and  $R^{1'}$  is methyl and  $R^2$  is hydrogen or nitro.

          In another preferred embodiment, when  $R^{2'}$  is isothiazole, preferably  $R^1$  and  $R^{1'}$  is methyl and  $R^2$  is hydrogen or nitro.

15           In another preferred embodiment, when  $R^{2'}$  is pyrrolidinyl, preferably,  $R^1$  is hydrogen or methyl,  $R^{1'}$  is hydrogen, methyl or methoxymethyl, and  $R^2$  is hydrogen, nitro, cyano, halogen, trifluoromethyl, or methoxy.

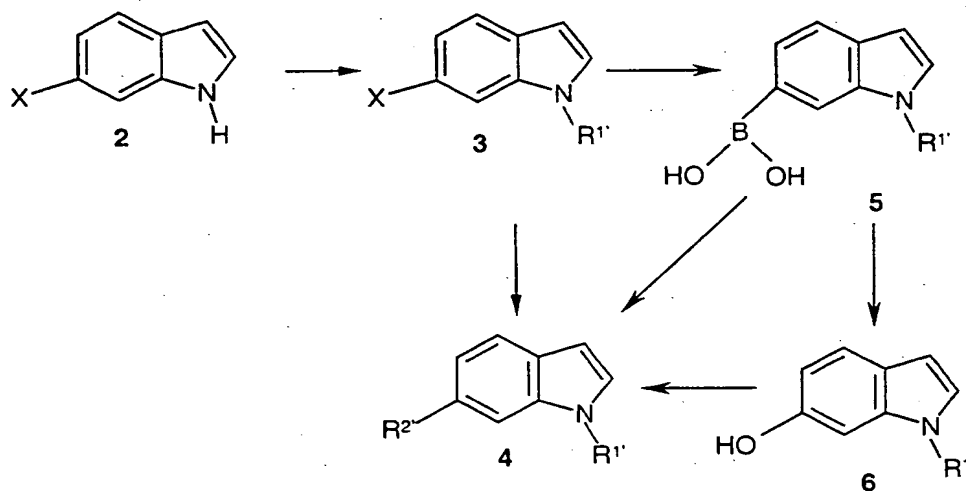
20           In another preferred embodiment, when  $R^{2'}$  is piperidinyl, preferably  $R^1$  and  $R^{1'}$  are both methyl and  $R^2$  is hydrogen.

25           In another preferred embodiment, when  $R^{2'}$  is morpholinyl, preferably  $R^1$  is hydrogen, methyl, preferably  $R^{1'}$  is methyl, hydrogen or methoxymethyl, and  $R^2$  is hydrogen, nitro, cyano, halogen, methyl, trifluoromethyl, or methoxy.

          In another preferred embodiment, when  $R^{2'}$  is ethoxy substituted by a heteroaryl or a heterocycle, preferably a heteroaryl and more preferably imidazolyl, preferably  $R^1$  and  $R^{1'}$  are both methyl and  $R^2$  is nitro.

30           The compounds of formula I are prepared as follows.

          The starting material, a compound of formula 4 can be prepared according to Scheme 1

**SCHEME I**

When  $R^2$  is heterocycle or heteroaryl and  $R^1$  is lower alkyl, compound 4 can be prepared according to Scheme 1.

10 A compound of formula 2, wherein X represents Br or I, is prepared by known methods (Moyer, M. P.; Shiurba, J.F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.), and is alkylated by known methods (NaH and alkyl iodide in N,N-dimethylformamide (DMF) or tetrahydrofuran at 0°C to about 25°C) to give a corresponding compound of formula 3. Alternatively, alkylation can be carried out using dimethyl carbonate and a base (such as  
15  $K_2CO_3$ ) or a catalyst (such as TBAB) in DMF, by heating the reaction mixture to reflux (greater than 90°C).

A compound of formula 3 is reacted with a heteroaryl substituted trialkylstannane, in a solvent such as toluene or THF in the presence of a base, such as triethylamine,  
20 catalyzed by a palladium catalyst, such as tetrakis(triphenylphosphine) palladium (0) at a temperature of 50°C to reflux to afford a corresponding compound of formula 4 with  $R^2$  being heteroaryl.

5           Alternatively, a compound of formula 3 is reacted with imidazole or substituted imidazole, in the presence of cesium carbonate, 1,10-phenanthroline and dibenzylideneacetone, catalyzed by copper(I) trifluoromethanesulfonate benzene complex, in a solvent such as xylene, at a temperature of 110-125°C to afford a corresponding compound of formula 4 with R<sup>2'</sup> being the imidazolyl with the nitrogen  
10       attached at the indole ring, as described in Kiyoori, A.; Marcoux, J-F.; Buchwald, S. L. *Tetrahedron letters*, **1999**, 40, 2657.

          When R<sup>2'</sup> is a heterocyclic amine such as pyrrolidinyl or morpholinyl, a compound of formula 4 can be prepared from a compound of formula 3 using Buchwald  
15       reaction. [Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, 62, 6066.] A compound of formula 3 is reacted with a heterocyclic amine, such as pyrrolidine, in the presence of sodium t-butoxide, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and 18-crown-6, catalyzed by tris(dibenzylideneacetone) dipalladium (0) in a solvent such as tetrahydrofuran, at a temperature of 25°C to 65°C to afford a compound of formula 4.

20

          When R<sup>2'</sup> is pyrimidinyl, a compound of formula 4 is prepared by the following sequence:

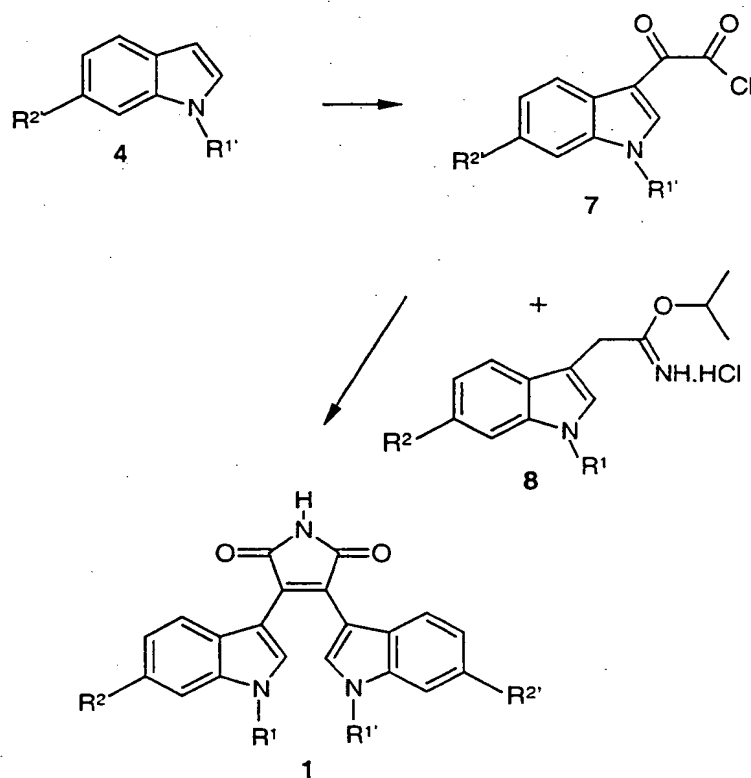
          A compound of formula 3 is reacted with n-butyllithium at -78°C in tetrahydrofuran followed by trialkylborate. The resulting product is then treated with  
25       aqueous methanol to give a compound of formula 5.

          A compound of formula 5 is reacted with bromopyrimidine, tetrakis(triphenylphosphine) palladium (0) in the presence of a base such as sodium carbonate in dioxane at a temperature of 100°-110° C to give a compound of formula 4  
30       with R<sup>2'</sup> being pyrimidinyl.

          When R<sup>2'</sup> is ethoxy substituted heterocycle or heteroaryl, such as 2-imidazol-1-yl-ethoxy, compound of formula 4 can be prepared by the following sequence:



- 5 A compound of formula 5 is reacted with hydrogen peroxide and sodium hydroxide to give compound 6. Treatment of compound 6 with 1-(2-hydroxyethyl)imidazol, triphenylphosphine and diethyl azodicarboxylate results in a compound of formula 4 with  $R^{2'}$  being 2-imidazol-1-yl-ethoxy.

**SCHEME 2**

10

A compound with formula 1 may be prepared according to Scheme 2, provided that when  $R^2$  and  $R^1$  are substituents which react with acid chlorides, such as, for example, alkyl amine, such substituent is protected with a conventional protecting group.

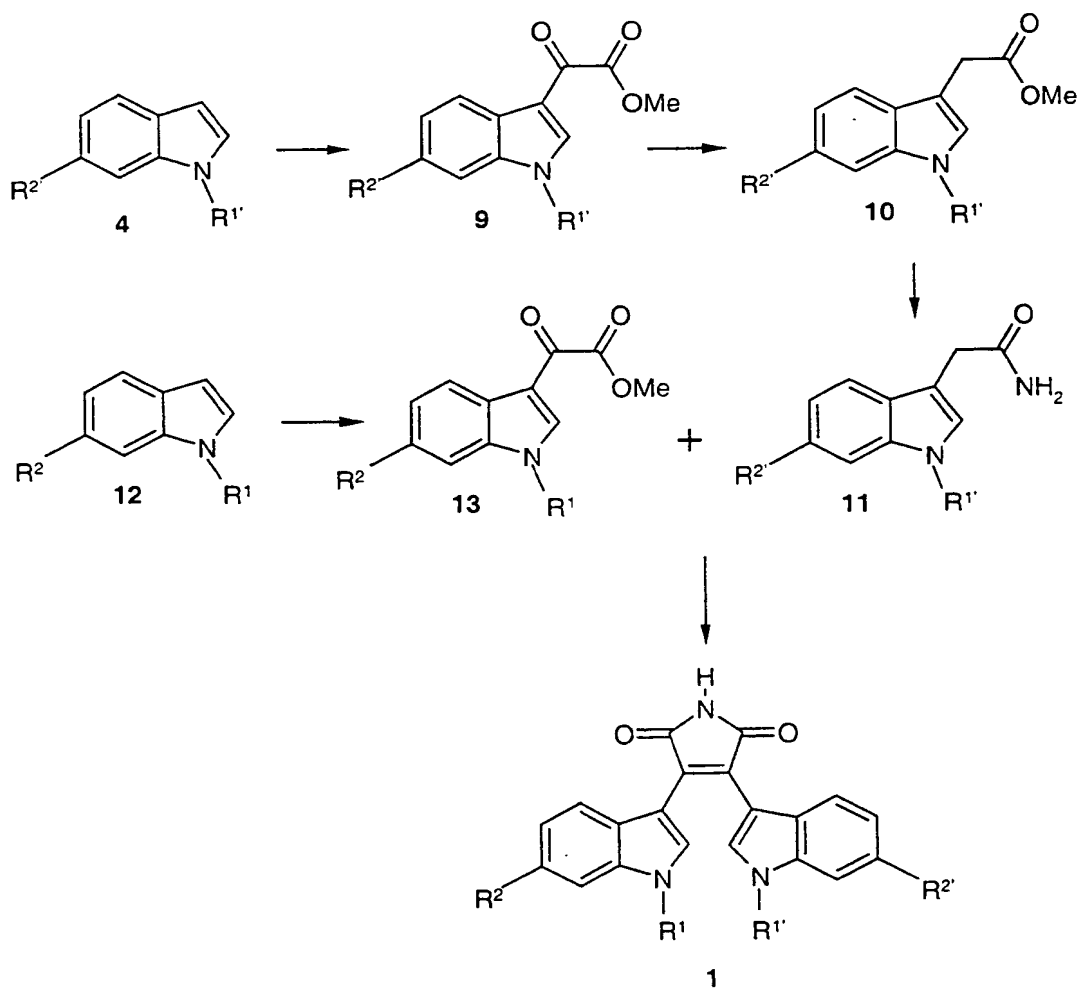
15

A compound of formula 4 is reacted with oxalyl chloride in a solvent such as diethyl ether or dichloromethane at a temperature of from  $0^\circ\text{C}$  to  $25^\circ\text{C}$  to form a corresponding compound of formula 7.

5

A compound of formula 7 is reacted with a compound of formula 8, a known compound (U.S. Patent No. 5,057,614) or a compound prepared by known methods, in the presence of a base, such as triethylamine in dichloromethane at a temperature between 0°C to 25°C. The resultant product is then treated with an acid, such as p-toluenesulfonic acid or hydrochloric acid in a solvent such as methylene chloride, methanol or THF at a temperature of 25°C to 65°C to form a corresponding compound of formula 1. If a protecting group was utilized during the reaction of 7 and 8, it is removed at this point using methods known in the art.

10

**SCHEME 3**

15

5

As set forth in Scheme 3, a compound of formula 4 is reacted with methyl oxalyl chloride in a solvent, such as diethyl ether or dichloromethane or without a solvent, at a temperature of 0°C to 25°C to form a compound of formula 9.

10

A compound of formula 9 is reacted with sodium hypophosphite hydrate, catalyzed by palladium on charcoal in a solvent such as dioxane at a temperature of 100°C to 110°C to afford a compound of formula 10.

15

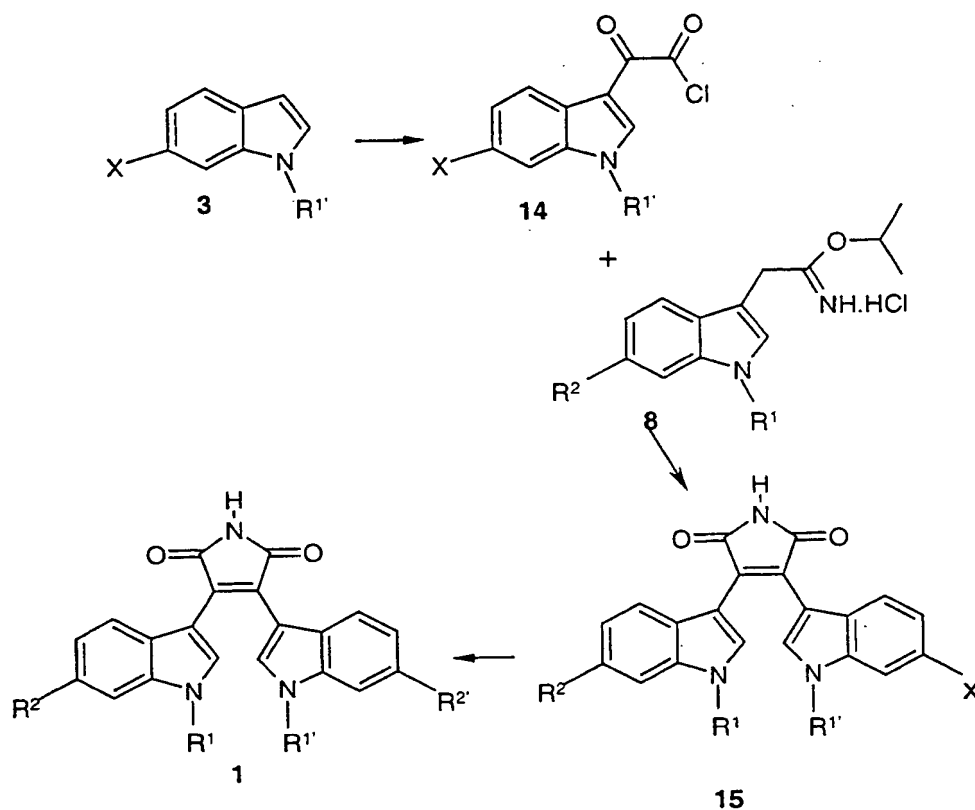
A compound of formula 10 is reacted with ammonium hydroxide to give a corresponding compound of formula 11.

20

A compound of formula 12 is reacted with methyl oxalyl chloride in a solvent, such as diethyl ether or dichloromethane or without a solvent, at a temperature of 0°C to 25°C to form a compound of formula 13.

25

A compound of formula 11 is reacted with a compound of formula 13 in the presence of a base, such as potassium t-butoxide, in a solvent such as tetrahydrofuran at a temperature of 0°C to 25°C. The resulting product is then treated with an acid, such as hydrochloric acid to give a compound of formula 1.

**SCHEME 4**

As set forth in Scheme 4, a compound with formula 3 is reacted with oxalyl chloride in a solvent such as diethyl ether or methylene chloride, at a temperature of 0°C to 25°C to afford a compound of formula 14.

10

A compound of formula 14 is reacted with a compound of formula 8 in the presence of a base, such as triethylamine in methylene chloride at a temperature between 0°C and 25°C. The resultant product is then treated with an acid, such as p-toluenesulfonic acid or hydrochloric acid in a solvent such as methylene chloride, methanol or THF at a temperature of 25°C to 65°C to form a compound of formula 15.

15

A compound with a formula 15 is reacted with a heteroaryl substituted trialkylstannane or boronic acid such as 2-(tributylstannyl) thiophene, or 2-(tributylstannyl) thioazole, thiophene-3-boronic acid, in the presence of a base such as

5 triethylamine or sodium carbonate, catalyzed by a palladium catalyst such as tetrakis(triphenylphosphine) palladium (0), or tri(dibenzylideneacetone) dipalladium (0), in a solvent such as toluene, acetonitrile, tetrahydrofuran, or dioxane, at a temperature of 80°C to 110°C to afford a compound with formula 1.

10 The conversion of an acidic compound of formula I into a pharmaceutically acceptable salt can be carried out by treatment with a suitable base in a known manner. Suitable salts are those derived not only from inorganic bases, for example, sodium, potassium or calcium salts, but also from organic bases such as ethylenediamine, monoethanolamine or diethanolamine. The conversion of a basic compound of formula I  
15 into a pharmaceutically acceptable salt can be carried out by treatment with a suitable acid in a known manner. Suitable salts are those derived not only from inorganic acids, for example, hydrochlorides, hydrobromides, phosphates or sulphates, but also from organic acids, for example, acetates, citrates, fumarates, tartrates, maleates, methansulphonates or p-toluenesulphonates.

20 The antiproliferative activity of the compounds of the invention is demonstrated below. These effects indicate that the compounds of the present invention are useful in treating cancer, in particular solid tumors such as breast and colon tumors.

25 The epithelial breast carcinoma cell line (MDAMB-435) was purchased from ATCC (American Type Cell Culture Collection) and was grown in culture medium as recommended by ATCC. For analysis of the effect of various compounds of formula I on the growth of these cells, the cells were plated at a concentration of 1500 cells/well in a 96 well tissue culture plate ("test plate"). The day after the cells were plated, the  
30 compounds to be analyzed were dissolved in 100% DMSO (dimethyl sulfoxide) to yield at 10mM stock solution. Each compound was diluted in H<sub>2</sub>O to 1mM and was added to triplicate wells in the first row of a 96 well master plate containing medium to yield a final concentration of 40μM. The compounds were then serially diluted in medium in the "master plate". The diluted compound(s) were then transferred to test plates containing  
35 cells. A row of vehicle "control cells" received DMSO. The final concentration of

- 5 DMSO in each well was 0.1%. 5 days post drug addition, the plate was analyzed as described below.

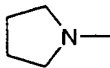
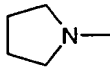
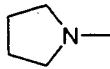
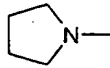
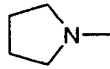
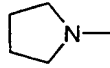
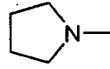
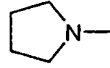
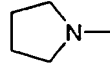
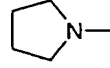
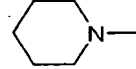
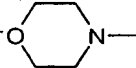
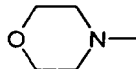
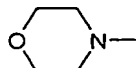

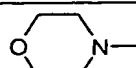
MTT (3-(4,5-methylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; thiazolyl blue) was added to each well to yield a final concentration of 1mg/ml. The plate was  
10 then incubated at 37°C for 2 1/2 - 3 hours. The MTT-containing medium was then removed and 50µl of 100% ethanol was added to each well to dissolve the formazan. The absorbences were then read using an automated plate reader (Bio-tek microplate reader). IC<sub>50</sub>s were calculated using the Reed and Munsch equation, *see* Am. J. Hygiene Vol. 27 pgs. 493-497, 1938.

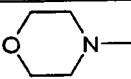
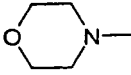
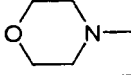
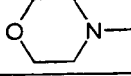
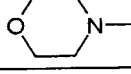
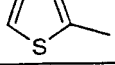
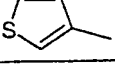
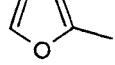
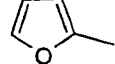
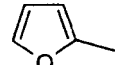
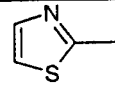
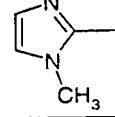
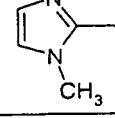
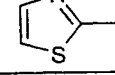
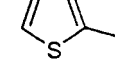
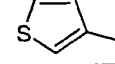
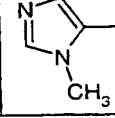
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The results of the foregoing *in vitro* experiments are set forth in Table I below.

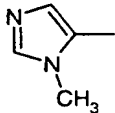
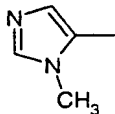
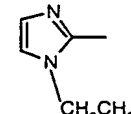
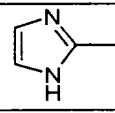
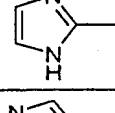
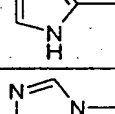
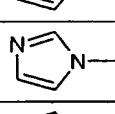
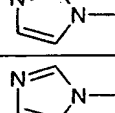
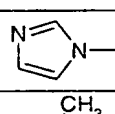
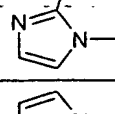
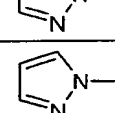
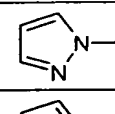
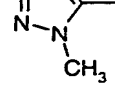


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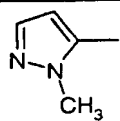
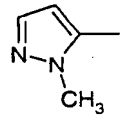
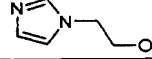
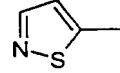
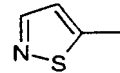
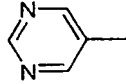
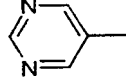
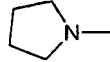
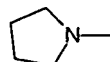
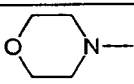
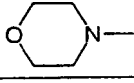
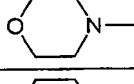
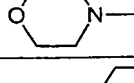
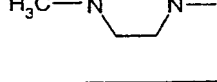
**TABLE I**

Example	R <sup>1</sup>	R <sup>1'</sup>	R <sup>2</sup>	R <sup>2'</sup>	IC <sub>50</sub> (μM)
12d	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.002
12h	CH <sub>3</sub>	H	NO <sub>2</sub>		0.002
12e	CH <sub>3</sub>	H	F		0.003
12f	CH <sub>3</sub>	H	Cl		<0.003
12g	CH <sub>3</sub>	CH <sub>2</sub> OCH <sub>3</sub>	NO <sub>2</sub>		0.02
14f	CH <sub>3</sub>	CH <sub>3</sub>	Br		0.005
14g	CH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>		0.04
14h	CH <sub>3</sub>	CH <sub>3</sub>	CF <sub>3</sub>		0.08
12j	CH <sub>3</sub>	CH <sub>3</sub>	H		0.06
15	CH <sub>3</sub>	CH <sub>3</sub>	CN		<0.01
12l	CH <sub>3</sub>	CH <sub>3</sub>	H		0.23
12a	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		<0.01
11	CH <sub>3</sub>	CH <sub>3</sub>	H		0.02
13	CH <sub>3</sub>	CH <sub>3</sub>	CN		0.004
14a	CH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>		0.02
14b	CH <sub>3</sub>	CH <sub>3</sub>	F		0.03

14c	CH <sub>3</sub>	CH <sub>3</sub>	Cl		0.002
14d	CH <sub>3</sub>	CH <sub>3</sub>	Br		0.003
14e	CH <sub>3</sub>	CH <sub>3</sub>	CF <sub>3</sub>		0.05
12b	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>		<0.01
12c	H	CH <sub>3</sub>	H		0.07
3	CH <sub>3</sub>	CH <sub>3</sub>	H		0.04
5	CH <sub>3</sub>	CH <sub>3</sub>	H		0.04
2g	CH <sub>3</sub>	CH <sub>3</sub>	H		0.02
2i	H	CH <sub>3</sub>	H		0.03
2h	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.01
4a	CH <sub>3</sub>	CH <sub>3</sub>	H		0.024
2c	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.03
4b	CH <sub>3</sub>	CH <sub>3</sub>	H		0.06
4c	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.02
4d	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.02
6	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.04
1	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.005



2a	CH <sub>3</sub>	CH <sub>3</sub>	H		0.05
2b	CH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>		0.06
2d	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.12
2e	CH <sub>3</sub>	CH <sub>3</sub>	H		0.08
2o	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.04
2f	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.02
7	CH <sub>3</sub>	CH <sub>3</sub>	H		0.06
8a	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.03
9	CH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>		0.06
10a	CH <sub>3</sub>	CH <sub>3</sub>	Br		0.025
10b	CH <sub>3</sub>	CH <sub>3</sub>	CN		0.03
8b	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.25
8c	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.02
8d	CH <sub>3</sub>	CH <sub>3</sub>	H		0.03
8e	CH <sub>3</sub>	CH <sub>3</sub>	Br		0.025
2j	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.2

2k	CH <sub>3</sub>	CH <sub>3</sub>	H		0.25
2l	CH <sub>3</sub>	CH <sub>3</sub>	Br		0.07
17	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.07
2m	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.01
2n	CH <sub>3</sub>	CH <sub>3</sub>	H		0.04
18	CH <sub>3</sub>	CH <sub>3</sub>	NO <sub>2</sub>		0.05
19	CH <sub>3</sub>	CH <sub>3</sub>	H		0.08
12i	H	CH <sub>3</sub>	H		0.08
14i	CH <sub>3</sub>	CH <sub>3</sub>	Cl		0.01
12m	CH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub>	F		0.17
12n	CH <sub>3</sub>	H	F		0.012
12o	CH <sub>3</sub>	H	H		0.037
16	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub>		1.18
12k	CH <sub>3</sub>	CH <sub>3</sub>	H		3.41

5

In an alternative embodiment, the present invention is directed to pharmaceutical compositions comprising at least one compound of formula I or a pharmaceutically acceptable salt thereof.

10

5           These pharmaceutical compositions can be administered orally, for example, in the form of tablets, coated tablets, dragees, hard or soft gelatin capsules, solutions, emulsions or suspensions. They can also be administered rectally, for example, in the form of suppositories. In particular, however, the compounds of the present invention are suitable for parenteral administration, for example, in the form of injection solutions.

10

          The pharmaceutical compositions of the present invention comprising compounds of formula I, prodrugs of such compounds, or the salts thereof, may be manufactured in a manner that is known in the art, *e.g.* by means of conventional mixing, encapsulating, dissolving, granulating, emulsifying, entrapping, dragee-making, or lyophilizing

15       processes. These pharmaceutical preparations can be formulated with therapeutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, steric acid or its salts can be used as such carriers for tablets, coated tablets, dragees and hard gelatin capsules. Suitable carriers for soft gelatin capsules include vegetable oils, waxes and fats. Depending on the nature of the active substance, no carriers are generally

20       required in the case of soft gelatin capsules. Suitable carriers for the manufacture of solutions and syrups are water, polyols, saccharose, invert sugar and glucose. Suitable carriers for injection are water, alcohols, polyols, glycerine, vegetable oils, phospholipids and surfactants. Suitable carriers for suppositories are natural or hardened oils, waxes, fats and semi-liquid polyols.

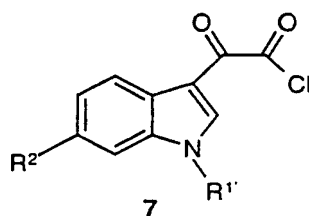
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          The pharmaceutical preparations can also contain preserving agents, solubilizing agents, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain other therapeutically valuable substances,

30       including additional active ingredients other than those of formula I.

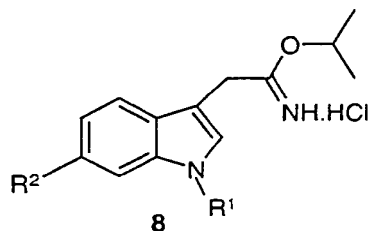
          As mentioned above, the present invention concerns also a process for the preparation of compounds of Formula I comprising

a) reacting a compound of formula 7 (scheme 2)



5

with a compound of formula 8 (scheme 2)



wherein R¹ and R¹' are independently are independently hydrogen or lower alkyl,  
lower alkenyl or lower alkynyl;

10

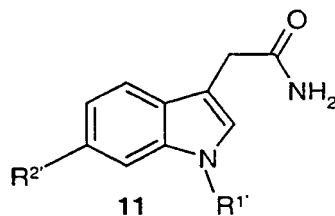
R² is hydrogen, nitro, cyano, halogen, lower alkyl, lower alkenyl, lower  
alkynyl, or lower alkoxy; and

R²' is a heteroaryl, heterocycle, ethyl substituted with a heteroaryl, or  
ethoxy substituted with a heteroaryl or heterocycle; or

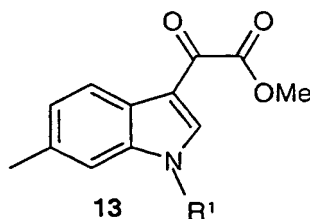
a pharmaceutically acceptable salt thereof,

15

b) reacting a compound of formula 11 (scheme 3)



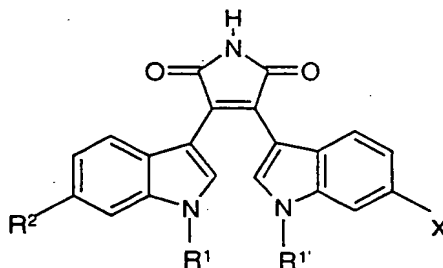
with a compound of formula 13 (scheme 3)



wherein  $R^1$  and  $R^{1'}$  are independently are independently hydrogen or lower alkyl,  
 lower alkenyl or lower alkynyl;  
 $R^2$  is hydrogen, nitro, cyano, halogen, lower alkyl, lower alkenyl, lower  
 alkynyl, or lower alkoxy; and  
 $R^2$  is a heteroaryl, heterocycle, ethyl substituted with a heteroaryl, or  
 ethoxy substituted with a heteroaryl or heterocycle; or  
 a pharmaceutically acceptable salt thereof,

or

c) reacting a compound of formula 15 (scheme 4)



wherein  $R^1$  and  $R^{1'}$  are independently are independently hydrogen or lower alkyl,  
 lower alkenyl or lower alkynyl;  
 $R^2$  is hydrogen, nitro, cyano, halogen, lower alkyl, lower alkenyl, lower  
 alkynyl, or lower alkoxy; and  
 $R^2$  is a heteroaryl, heterocycle, ethyl substituted with a heteroaryl, or  
 ethoxy substituted with a heteroaryl or heterocycle; or  
 a pharmaceutically acceptable salt thereof,  
 and X is Br or I,

with a heteroaryl substituted trialkylstannane or boronic acid in the presence of a  
 base catalyzed by a palladium catalyst.

As mentioned above, the compounds of the present invention are useful in the  
 treatment or control of cell proliferative disorders, in particular oncological disorders.  
 These compounds and formulations containing said compounds are particularly useful in  
 the treatment or control of solid tumors, such as, for example, breast and colon tumors.

5      Accordingly, the present invention comprises the use of the above compounds for the preparation of medicaments, especially for the treatment or control of cell proliferative disorders, in particular oncological disorders, e.g. for the treatment or control of solid tumors, such as, for example, breast and colon tumors.

10            A therapeutically effective amount of a compound in accordance with this invention means an amount of compound that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is within the skill in the art.

15            The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, in the case of oral or parenteral administration to adult humans weighing approximately 70 Kg, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 200 mg to about 1,000 mg, should be appropriate, although the  
20      upper limit may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration, it may be given as continuous infusion.

5

**Examples**

The compounds of the present invention may be synthesized according to known techniques, such as, for example, the general schemes provided above. The following examples illustrate preferred methods for synthesizing the compounds and formulations of the present invention.

**Example 1****3-[1-Methyl-6-(3-methyl-3H-imidazol-4-yl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione**

- 15 a) 6-Bromoindole (10.4 g, 53.1 mmol) (prepared according to Moyer, M. P.; Shiurba, J.F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.) was added in small portions over 30 min to a stirred suspension of sodium hydride (2.96 g, 61.7 mmol, 50% in mineral oil) in dry THF (120 mL) at 0°C. Stirring was continued for another 30 min. Iodomethane (4.5 ml, 71.6 mmol) was added dropwise. After 20 1h, the mixture was poured into ice-water and extracted with ether (3 x 200 mL). The combined organic extracts were washed with brine and dried (MgSO<sub>4</sub>). Evaporation of the solvents and chromatography of the residue over silica gel using hexane gave 6-bromo-1-methyl-1H-indole (10.8 g, 97%).
- 25 b) A solution of 6-bromo-1-methyl-1H-indole (6.2 g, 29.5 mmol) in toluene was degassed by bubbling argon through the solution for 10-20 min. Et<sub>3</sub>N (8.2 mL, 59 mmol), tetrakis(triphenylphosphine)palladium (0) (681 mg, 0.59 mmol) and 1-methyl-5-(tributylstannyl)imidazole (Gaare, K.; Repstad, T.; Benneche, T.; Undheim, K. *Acta Chem. Scan.* **1993**, *47*, 57.) (11.6 g, 31.2 mmol) in toluene (30 30 mL) were added and the mixture was heated to 120°C for 18 h until Pd black appeared. The mixture was cooled, filtered through a pad of silica gel and the pad was washed well with EtOAc. The filtrate was evaporated and chromatography of the residue over silica gel using 0.5-1% methanol in EtOAc gave 1-methyl-6-(3-methyl-3H-imidazol-4-yl)-1H-indole (5.21 g, 84%) as an off white crystalline 35 solid.

5 c) 1-Methyl-6-(3-methyl-3H-imidazol-4-yl)-1H-indole (5.0 g, 23.7 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) (dried under 3A° molecular sieves) at 0°C. A solution of oxalyl chloride in CH<sub>2</sub>Cl<sub>2</sub> (2 M, 23.7 mL, 47.4 mmol) was added dropwise over 10 min. The mixture was stirred at 0°C for 2.5 h and evaporated. Ether (25 mL) was added to the solid residue and the mixture was stirred for 30  
10 min. The resulting yellow solid was filtered off, washed with ether and dried under vacuum for 30 min. 2-(1-Methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride (7.02 g, 22.5 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (200 mL) were added to the yellow solid at 0°C. Et<sub>3</sub>N (dried over 3A° molecular sieves) (16.5 mL, 118.6 mmol) was added dropwise over 10 min., and the orange-red mixture  
15 was stirred at room temperature overnight. The mixture was diluted with CHCl<sub>3</sub> and washed with aqueous Na<sub>2</sub>CO<sub>3</sub>. The aqueous layer was back extracted with CHCl<sub>3</sub>. The combined organic extracts were washed with brine, dried (K<sub>2</sub>CO<sub>3</sub>) and evaporated. MeOH (150 mL) and concentrated HCl (37%, 10 mL) were added. The mixture was heated at reflux for 2h, then cooled, diluted with CHCl<sub>3</sub>  
20 and washed with aqueous Na<sub>2</sub>CO<sub>3</sub>. The aqueous layer was back extracted with CHCl<sub>3</sub>. The combined organic extracts were washed with brine and dried (K<sub>2</sub>CO<sub>3</sub>). The mixture was passed through a pad of silica gel (10 x 10 cm) and the pad was washed with 10% methanol/EtOAc. Evaporation of the combined filtrates gave the crude product as an orange solid. Crystallization of the product  
25 from EtOH /CHCl<sub>3</sub> gave 3-[1-methyl-6-(3-methyl-3H-imidazol-4-yl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione (5.65 g, 49%) as an orange solid.

### Example 2

30 In a manner similar to that described in Example I, the following compounds were prepared. The starting materials were prepared in a manner analogous to that described in 1(a) and 1(b).

a) 3-(1-Methyl-1H-indol-3-yl)-4-[1-methyl-6-(3-methyl-3H-imidazol-4-yl)-1H-indol-3-yl]pyrrole-2,5-dione (391 mg, 45%) was prepared as an orange solid  
35



- 5 using 1-methyl-6-(3-methyl-3H-imidazol-4-yl)-1H-indole (422 mg, 2 mmol) and 1-methyl-3-indoleacetimidic acid isopropyl ester hydrochloride (530 mg, 2 mmol).
- 10 b) 3-(6-Methoxy-1-methyl-1H-indol-3-yl)-4-[1-methyl-6-(3-methyl-3H-imidazol-4-yl)-1H-indol-3-yl]pyrrole-2,5-dione (78 mg, 11%) was prepared as a dark brown solid using 1-methyl-6-(3-methyl-3H-imidazol-4-yl)-1H-indole (316 mg, 1.5 mmol) and 2-(1-methyl-6-methoxy-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride (445 mg, 1.5 mmol).
- 15 c) 3-[1-Methyl-6-(1-methyl-1H-imidazol-2-yl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione (1.08 g, 34%) was prepared as an orange solid from 6-(1-methyl-1H-imidazol-2-yl)-1-methyl-1H-indole and 2-(1-methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride.
- 20 d) 3-[6-(1-Ethyl-1H-imidazol-2-yl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione (155 mg, 38%) was prepared using 6-(1-ethyl-1H-imidazol-2-yl)-1-methyl-1H-indole (185 mg, 0.82 mmol) and 2-(1-methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride (256 mg, 0.82 mmol).
- 25 e) 3-[6-(1H-Imidazol-2-yl)-1-methyl-1H-indol-3-yl]-4-(1-methyl-1H-indol-3-yl)pyrrole-2,5-dione (37 mg, 14%) was prepared as an orange solid using 1-methyl-6-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-1H-indole (200 mg, 0.61 mmol) and 1-methyl-3-indoleacetimidic acid isopropyl ester hydrochloride (162 mg, 0.61 mmol) followed by deprotection using 20% HCl in refluxing EtOH.
- 30 f) 3-[6-(3H-Imidazol-4-yl)-1-methyl-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione hydrochloride (45mg, 18%) was prepared from 1-methyl-6-[3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-1H-indole (160 mg, 0.49 mmol) and 2-(1-methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl

- 5 ester hydrochloride (156 mg, 0.5 mmol) followed by deprotection using 20% HCl in refluxing EtOH.
- g) 3-(6-Furan-2-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)pyrrole-2,5-dione (51 mg, 27%) was prepared as an orange solid using 6-furan-2-yl-1-methyl-1H-indole (100 mg, 0.5 mmol) and 1-methyl-3-indoleacetimidic acid isopropyl ester hydrochloride (120 mg, 0.45 mmol).
- 10 h) 3-(6-Furan-2-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione (70 mg, 40%) was prepared using 6-furan-2-yl-1-methyl-1H-indole (100 mg, 0.5 mmol) and 2-(1-methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride (117 mg, 0.38 mmol).
- 15 i) 3-(6-Furan-2-yl-1-methyl-1H-indol-3-yl)-4-(1H-indol-3-yl)pyrrole-2,5-dione was prepared from 6-furan-2-yl-1-methyl-1H-indole and 2-[1-(2,2-dimethylpropionyl)-1H-indol-3-yl]acetimidic acid isopropyl ester hydrochloride followed by deprotection with NaOMe in methanol.
- 20 j) 3-[1-Methyl-6-(2-methyl-2H-pyrazol-3-yl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione was prepared from 1-methyl-6-(2-methyl-2H-pyrazol-3-yl)-1H-indole and 2-(1-methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride.
- 25 k) 3-(1-Methyl-1H-indol-3-yl)-4-[1-methyl-6-(2-methyl-2H-pyrazol-3-yl)-1H-indol-3-yl]pyrrole-2,5-dione was prepared from 1-methyl-6-(2-methyl-2H-pyrazol-3-yl)-1H-indole and 2-(1-methyl-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride.
- 30 l) 3-(6-Bromo-1-methyl-1H-indol-3-yl)-4-[1-methyl-6-(2-methyl-2H-pyrazol-3-yl)-1H-indol-3-yl]pyrrole-2,5-dione was prepared from 1-methyl-6-(2-methyl-2H-

- 5 pyrazol-3-yl)-1H-indole and 2-(6-bromo-1-methyl-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride.
- m) 3-(6-Isythiazol-5-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2, 5-dione was prepared from 6-isothiazol-5-yl-1-methyl-1H-indole and  
10 2-(1-methyl-6-nitro-1H-indol-3-yl)-acetimidic acid isopropyl ester hydrochloride.
- n) 3-(6-Isythiazol-5-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione was prepared from 6-isothiazol-5-yl-1-methyl-1H-indole and 2-(1-methyl-1H-indol-3-yl)-acetimidic acid isopropyl ester hydrochloride.
- 15 o) 3-[6-(1H-Imidazol-2-yl)-1-methyl-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2, 5-dione was prepared from 1-methyl-6-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-1H-indole and 2-(1-methyl-6-nitro-1H-indol-3-yl)-acetimidic acid isopropyl ester hydrochloride followed by deprotection using  
20 aqueous hydrochloric acid in ethanol.

### Example 3

#### **3-(1-Methyl-1H-indol-3-yl)-4-(1-methyl-6-thiophen-2-yl-1H-indol-3-yl)pyrrole-2,5-dione**

25 To a solution of 3-(6-bromo-1-methyl-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)pyrrole-2,5-dione as prepared in Example 2 (108 mg, 0.25 mmol) in dry THF(5 mL) was added tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol), 2-(tributylstannyl) thiophene (0.12 mL, 0.375 mmol) and triethylamine (0.10 mL, 0.70 mmol). The mixture was heated under reflux for 3 days and cooled to room  
30 temperature. Evaporation of the solvents and chromatography of the crude product over silica gel using 30% EtOAc in hexane gave 3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-thiophen-2-yl-1H-indol-3-yl)-pyrrole-2,5-dione (72 mg, 66%).

35

5

**Example 4**

In a manner similar to that described in Example 3, the following compounds were prepared.

- 10 a) 3-(1-Methyl-1H-indol-3-yl)-4-(1-methyl-6-thiazol-2-yl-1H-indol-3-yl)pyrrole-2,5-dione (25 mg, 23%) was prepared from 3-(6-bromo-1-methyl-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione (108 mg, 0.25 mmol) and 2-(tributylstannyl)thioazole (140 mg, 0.375 mmol).
- 15 b) 3-(1-Methyl-1H-indol-3-yl)-4-[1-methyl-6-(1-methyl-1H-imidazol-2-yl)-1H-indol-3-yl]-pyrrole-2,5-dione (46 mg, 38%) was prepared from 3-(6-bromo-1-methyl-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)pyrrole-2,5-dione (120 mg, 0.28 mmol) and 1-methyl-2-(tributylstannyl)imidazole (0.8 mL, containing 50% 1-methyl-imidazole) (Molloy, K. C.; Waterfield, P. C.; Mahon, M. F. J. *Organometallic. Chem.* **1989**, 365, 61.)
- 20 c) 3-(1-Methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-thiazol-2-yl-1H-indol-3-yl)pyrrole-2,5-dione (21 mg, 23%) was prepared from 3-(6-iodo-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione (100 mg, 0.19 mmol) and 2-(tributylstannyl)thioazole (0.107 mL).
- 25 d) 3-(1-Methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-thiophen-2-yl-1H-indol-3-yl)-pyrrole-2,5-dione (180 mg, 37%) was prepared from 3-(6-iodo-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione (525 mg, 1 mmol) and 2-(tributylstannyl)thiophene (0.98 mL, 3.09 mmol).

30

**Example 5**

**3-(1-Methyl-1H-indol-3-yl)-4-(1-methyl-6-thiophen-3-yl-1H-indol-3-yl)pyrrole-2,5-dione**

5 Argon was bubbled through a solution of 3-(6-bromo-1-methyl-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)pyrrole-2,5-dione (160 mg, 0.37 mmol) in dioxane (15 mL) for 10 min. Tetrakis(triphenylphosphine)palladium (0) (8.5 mg, 0.007 mmol) and thiophene-3-boronic acid (52 mg, 0.41 mmol) and aqueous Na<sub>2</sub>CO<sub>3</sub> (0.37 mL, 2M) were added. The mixture was refluxed for 2 h and more  
10 tetrakis(triphenylphosphine)palladium (0) (20 mg, 0.01 mmol) was added. Refluxing was continued for 24 h. The mixture was cooled and evaporated. Chromatography of the residue over silica using 50% EtOAc in hexane gave 3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-thiophen-3-yl-1H-indol-3-yl)pyrrole-2,5-dione (117 mg, 72%).

15

#### Example 6

In a manner similar to that described in Example 5, 3-(1-methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-thiophen-3-yl-1H-indol-3-yl)pyrrole-2,5-dione (11 mg, 12%) was prepared from 3-(6-iodo-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (100 mg, 0.19 mmol) and thiophene-3-boronic acid (49 mg, 0.38 mmol).  
20

#### Example 7

3-(6-Imidazol-1-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)pyrrole-2,5-dione  
25

a) An oven-dried re-sealable Schlenk tube was flushed with argon and charged with copper(I) trifluoromethanesulfonate benzene complex (1.39 g, 2.76 mmol), 1,10-phenanthroline (5.69 g, 31.6 mmol), dibenzylideneacetone (740 mg, 3.16 mmol) and cesium carbonate (10 g, 30.7 mmol). Imidazole (3.23 g, 44.8 mmol), 6-iodo-1-methyl-1H-indole (8.13 g, 31.6 mmol) and xylene (16 mL) were added and the  
30 tube was purged with argon. The tube was sealed and heated with stirring at 160°C for 18 h. The mixture was cooled to room temperature and partitioned between CH<sub>2</sub>Cl<sub>2</sub> (35 mL) and saturated aqueous NH<sub>4</sub>Cl (5 mL). The organic layer was separated and washed with brine. Then the organic extract was dried over  
35

5           MgSO<sub>4</sub>, filtered and concentrated. The crude concentrate was filtered through a pad of silica gel and evaporated. Purification by HPLC afforded 6-imidazol-1-yl-1-methyl-1H-indole as a brown oil (3.1 g, 50%).

[Ref: Kiyoori, A.; Marcoux, J-F.; Buchwald, S. L. *Tetrahedron Lett.*, **1999**, *40*, 2657.]

10

b)       6-Imidazol-1-yl-1-methyl-1H-indole (7.0g, 35.5 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) (dried under 3A molecular sieves) at 0°C. A solution of oxalyl chloride in CH<sub>2</sub>Cl<sub>2</sub> (2 M, 35.5 mL, 71 mmol) was added dropwise over 10 min. The mixture was stirred at 0°C for 1.5 h and evaporated. Ether (100 mL) was added to the solid residue and after the mixture was stirred for 30 min, the resulting yellow solid was filtered off, washed with ether and dried under vacuum for 30 min. 1-Methyl-3-indoleacetimidic acid isopropyl ester hydrochloride (9.6 g, 36 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (200 mL) were added to the yellow solid at 0°C. Et<sub>3</sub>N (dried over 3A° molecular sieves) (30 mL) was added dropwise over 10 min. The orange-red mixture was stirred at room temperature overnight. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (300 mL) and washed with aqueous Na<sub>2</sub>CO<sub>3</sub> (2 x 200 mL). The aqueous layer was back extracted with CH<sub>2</sub>Cl<sub>2</sub> (100mL). The combined organic extracts were washed with brine, dried (K<sub>2</sub>CO<sub>3</sub>) and evaporated. MeOH (100 mL) and concentrated HCl (37%, 10 mL) were added and the mixture was heated at reflux for 2h. The reaction mixture was cooled, diluted with water (200 mL) and EtOAc (200 mL). The mixture was made basic using solid K<sub>2</sub>CO<sub>3</sub> and extracted with EtOAc (4 x 200 mL). The combined organic extracts were washed with aqueous Na<sub>2</sub>CO<sub>3</sub> (2 x 200 mL) brine and dried (K<sub>2</sub>CO<sub>3</sub>). The mixture was passed through a pad of silica gel (10 x 10 cm) and the pad was washed with 10% methanol in EtOAc. Evaporation of the combined eluates gave the crude product as an orange solid. Recrystallization of the crude product using EtOAc, MeOH and CHCl<sub>3</sub> gave 3-(6-imidazol-1-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione (5.0 g, 33%) as an orange solid.

5

**Example 8**

In a manner similar to that described in example 7, the following compounds were prepared. The starting materials were prepared in a manner analogous to that described in example 7

10

a) 3-(6-Imidazol-1-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione ( 5.60 g, 64%) was prepared from 6-imidazol-1-yl-1-methyl-1H-indole (3.70 g, 18.7 mmol) and 2-(1-methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride (5.80 g, 18.7 mmol).

15

b) 3-[1-Methyl-6-(2-methyl-imidazol-1-yl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (23 mg, 5.5%) was prepared from 2-(1-methyl-6-(2-methyl-imidazol-1-yl)-1H-indole (260 mg, 0.87 mmol) and 2-(1-methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride (271 mg, 0.87 mmol).

20

c) 3-(1-Methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-pyrazol-1-yl-1H-indol-3-yl)pyrrole-2, 5-dione was prepared from 1-methyl-6-pyrazol-1-yl-1H-indole and 2-(1-methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride.

25

d) 3-(1-Methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrazol-1-yl-1H-indol-3-yl)pyrrole-2, 5-dione was prepared from 1-methyl-6-pyrazol-1-yl-1H-indole and 2-(1-methyl-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride.

30

e) 3-(6-Bromo-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrazol-1-yl-1H-indol-3-yl)pyrrole-2,5-dione was prepared from 1-methyl-6-pyrazol-1-yl-1H-indole and 2-(6-bromo-1-methyl-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride.

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5

**Example 9****3-(6-Imidazol-1-yl-1-methyl-1H-indol-3-yl)-4-(6-methoxy-1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione**

- 10 a) 6-Imidazol-1-yl-1-methyl-1H-indole (0.90 g, 4.56 mmol ) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and cooled at 0°C. Methyl chlorooxoacetate (1.3 mL, 14 mmol) was added. Stirring was continued for 2 h at 0°C and more methyl chlorooxoacetate (0.4 mL, 4.3 mmol) was added. After an additional 2 h, the solvent was removed. The residual solid was taken up in ether, filtered and  
15 washed well with ether to give crude methyl (6-imidazol-1-yl-1-methyl-1H-indol-3-yl)glyoxylate (1.50 g).
- b) Crude methyl (6-imidazol-1-yl-1-methyl-1H-indol-3-yl)glyoxylate (1.40 g) in dioxane (100 mL) in a 250 mL round bottom flask was fitted with a reflux  
20 condenser and a balloon on the top. The system was flushed with argon then Pd/C (140 mg, 10%) was added, followed by sodium hypophosphite hydrate (7.2 g) in water (10mL) and the mixture was heated under reflux overnight. More sodium hypophosphite hydrate (3.0 g) in water (5 mL) and Pd/C (50 mg) were added. The mixture was refluxed for an additional 5 h, and cooled. The solvents  
25 were evaporated and the residue was diluted with EtOAc (100 mL). The solution was carefully washed with aqueous NaHCO<sub>3</sub> (2 x 100 mL). The combined aqueous layers were back extracted with EtOAc (2 x 200 mL). The combined organic extracts were filtered through a pad of silica gel and a layer of MgSO<sub>4</sub> on the top and the pad was washed with 10% methanol in CH<sub>2</sub>Cl<sub>2</sub>. The combined  
30 filtrate were evaporated and chromatography of the residue over silica gel using 1-6 % methanol in CH<sub>2</sub>Cl<sub>2</sub> gave (6-imidazol-1-yl-1-methyl-1H-indolyl-3-yl)acetic acid methyl ester (230 mg, 17%).
- c) (6-Imidazol-1-yl-1-methyl-1H-indol-3-yl)acetic acid methyl ester (230 mg, 0.85  
35 mmol) was suspended in concentrated NH<sub>4</sub>OH (5 mL) in a 100 mL flask and



- 5 stirred in a sealed flask for 24h. Lyophilization of the mixture gave a crude product, which was chromatographed on silica gel using 2-8% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to give (6-imidazol-1-yl-1-methyl-1H-indol-3-yl)acetamide (145 mg, 67%).
- 10 d) 6-Methoxy-1-methyl-1H-indole (1.0 g, 6.19 mmol) was dissolved in ether (10mL) and cooled to 0°C. Methyl chlorooxoacetate (1.17 mL, 12.4 mmol) was added dropwise. Stirring was continued at 0°C for 6 h. The mixture was filtered and washed well with ether to give methyl (6-methoxy-1-methyl-1H-indol-3-yl)glyoxylate (621 mg, 41%).
- 15 f) A solution of *t*-BuOK in THF (1 M, 0.53 mL, 0.53 mmol) was added dropwise to a mixture of methyl (6-methoxy-1-methyl-1H-indolyl-3)glyoxylate (47 mg, 0.18 mmol) and (6-imidazol-1-yl-1-methyl-1H-indol-3-yl)acetamide (46 mg, 0.18 mmol) at 0°C. The cooling bath was removed after 15 min and the mixture was stirred at room temperature for 3 h. Concentrated hydrochloric acid (1mL) was
- 20 added and the mixture was stirred for 30 min. Then the mixture was made basic with aqueous NaHCO<sub>3</sub> and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with aqueous NaHCO<sub>3</sub> and dried (K<sub>2</sub>CO<sub>3</sub>). The extracts were filtered through a pad of silica gel and the pad was washed with 5% MeOH in EtOAc. Evaporation of the solvents and chromatography of the residue
- 25 over silica gel using 70% EtOAc in hexanes and then EtOAc gave 32 mg of an orange solid which was then dissolved in 1:1 MeOH/ CH<sub>2</sub>Cl<sub>2</sub> (1mL) and diluted with ether (8 mL). The resulting precipitate was filtered and washed with 1:1 ether/hexane (8 mL) to give 3-(6-imidazol-1-yl-1-methyl-1H-indol-3-yl)-4-(6-methoxy-1-methyl-1H-indol-3-yl)pyrrole-2,5-dione (29 mg, 36%). (RO 28-4240)
- 30 Faul, M.M.; Winneroski, L.L.; Krumrich, C.A. *J. Org. Chem.* 1998, 63, 6053.

### Example 10

5 In a manner similar to that described in Example 9 the following compounds were prepared. The starting materials were prepared in a manner analogous to that described in 9(c) and (d).

- 10 a) 3-(6-Bromo-1-methyl-1H-indol-3-yl)-4-(6-imidazol-1-yl-1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione (13 mg, 19%): prepared from methyl (6-bromo-1-methyl-1H-indol-3)glyoxylate (43 mg, 0.14 mmol) and (6-imidazol-1-yl-1-methyl-1H-indol-3-yl)acetamide (50 mg, 0.20 mmol).
- 15 b) 3-[4-(6-Imidazol-1-yl-1-methyl-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-1-methyl-1H-indole-6-carbonitrile (14 mg, 16%): prepared from methyl (6-cyano-1-methyl-1H-indol-3)glyoxylate (44 mg, 0.18 mmol) and (6-imidazol-1-yl-1-methyl-1H-indol-3-yl)-acetamide (46 mg, 0.18 mmol).

#### Example 11

20 **3-(1-Methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole 2,5-dione**

- 25 a) An oven dried flask was flushed with argon and charged with 18-crown-6 (15 g, 56.7 mmol), 6-iodo-1-methyl-1H-indole (10.4 g, 40.46 mmol), morpholine (4.3 mL, 48.6 mmol), sodium *t*-butoxide (5.42 g, 54.7 mmol), tris(dibenzylidene acetone)dipalladium (0) (186 mg, 0.20 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (380 mg, 0.61 mmol). The flask was flushed with argon for 10 min and dry THF (80 mL) was added. The mixture was stirred at room temperature for 5 h, then diluted with ether and washed with brine. The organic layer was dried (MgSO<sub>4</sub>), evaporated and the crude product was purified by chromatography on silica gel using 5-30% ether / hexanes to give 1-methyl-6-morpholin-4-yl-1H-indole (8.17 g, 94%).
- 30

[Ref: Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066.]

5           6-Iodo-1-methyl-1H-indole was prepared in a similar manner as described in example 1(a).

10           b)   A solution of 1-methyl-6-morpholin-4-yl-1H-indole (0.50 g, 2.31 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) (dried over  $3\text{\AA}$  molecular sieves) was cooled to  $0^\circ\text{C}$ . Oxalyl chloride (0.4 mL, 4.62 mmol), was added dropwise over 5 min. The mixture was stirred at  $0^\circ\text{C}$  for 4 h and evaporated. The residual solid was triturated with ether, filtered, washed with ether and dried under vacuum for 30 min. 1-Methyl-3-indoleacetimidic acid isopropyl ester hydrochloride (0.58 g, 2.20 mmol) and  $\text{CH}_2\text{Cl}_2$  (9 mL) were added to the yellow solid at  $0^\circ\text{C}$ .  $\text{Et}_3\text{N}$  (dried over  $3\text{\AA}$  molecular sieve) (1.8 mL) was added dropwise over 10 min. and then the orange-red mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with 1 N NaOH and the aqueous layer was back-extracted with EtOAc. The combined organic extracts were washed with brine, dried ( $\text{K}_2\text{CO}_3$ ) and evaporated. The residue was dissolved in MeOH (100 mL) containing  $\text{TsOH}\cdot\text{H}_2\text{O}$  (3.30 g, 17.3 mmol) and the mixture was stirred at room temperature for 4 h. After the solvents were removed under reduced pressure the residue was diluted with EtOAc (500 mL) and made basic using aqueous  $\text{NaHCO}_3$ . The organic layer was separated and the aqueous layer was back extracted with EtOAc. The combined organic extracts were washed with brine, dried ( $\text{MgSO}_4$ ), and evaporated. Chromatography of the residue over silica gel using 30-70% EtOAc / hexanes gave 3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole 2,5-dione (0.30 g, 30%) as an orange solid.

### Example 12

30

In a manner similar to that described in Example 11 the following compounds were prepared. The starting materials were prepared in a manner analogous to that described in 11 (a).

- 5 a) 3-(1-Methyl-6-morpholin-4-yl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione (315 mg, 25%): prepared from 1-methyl-6-morpholin-4-yl-1H-indole (0.56g, 2.56 mmol) and 2-(1-methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride (0.81 g, 2.56 mmol).
- 10 b) 3-(1,6-Dimethyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2, 5-dione: prepared from 1,6-dimethyl-1H-indole and 2-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)-acetimidic acid isopropyl ester hydrochloride.
- 15 c) 3-(1H-Indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2, 5-dione: prepared from 1-methyl-6-morpholin-4-yl-1H-indole and 2-[1-(2,2-dimethyl-propionyl)-1H-indol-3-yl]acetimidic acid isopropyl ester hydrochloride followed by deprotection using sodium methoxide in methanol.
- 20 d) 3-(1-Methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione (0.96g, 28%): prepared as a dark brown solid using 1-methyl-6-pyrrolidin-1-yl-1H-indole (1.60 g, 8 mmol), and 2-(1-methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride (2.24 g, 7.2 mmol).
- 25 e) 3-(6-Fluoro-1-methyl-1H-indol-3-yl)-4-(6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2, 5-dione was prepared from 6-pyrrolidin-1-yl-1H-indole and 2-(6-fluoro-1-methyl-1H-indol-3-yl)-acetimidic acid isopropyl ester hydrochloride.

6-Pyrrolidin-1-yl-1H-indole was prepared as follows:

- 30 a) A mixture of 1-methyl-6-nitro-1H-indole (5.0 g, 28.4 mmol) and 10% Pd/C(1.0 g) in ethanol (200 ml) and tetrahydrofuran (100 ml) was hydrogenated at atmospheric pressure for 14 hours. The reaction mixture was filtered and concentrated to give 1-methyl-6-amino-1H-indole after crystallization from ether/hexane (3.8 g, 80%).

- 5     b)     A mixture of 1-methyl-6-amino-1H-indole (11 g, 83 mmol) and succinic anhydride (8.3 g, 83 mmol) in toluene (150 ml) was heated to reflux for 1 hour. The reaction mixture was cooled and evaporated to give a solid (18.0). A mixture of resulting solid (10.1 g) and sodium acetate (3.45 g, 42 mmol) in acetic anhydride (36 mL) was heated at reflux for 15 minutes. The reaction mixture was cooled to room temperature and ice-water was added slowly to it. The mixture was stirred for 15 minutes and extracted with ethyl acetate-tetrahydrofuran. The combined organic extracts were washed with brine and dried over magnesium sulfate. Evaporation of the solvent gave a crude product, which was further purified by recrystallizing in ethyl acetate-hexanes to give (1-methyl-1H-indol-6-yl)-pyrrolidine-2, 5-dione (6.0 g).
- 10
- 15
- c)     1-(1-Methyl-1H-indol-6-yl)-pyrrolidine-2,5-dione (3.8 g, 17.7 mmol) in tetrahydrofuran (75 ml) was treated with lithium aluminum hydride in tetrahydrofuran (88 ml, 1.0 M, 88 mmol) for 2 hours at room temperature. The mixture was cooled and treated with aqueous sodium sulfate. The mixture was extracted with ether and the organic layer was concentrated. Chromatography of the crude product over silica gel with 70% hexane/ethyl acetate gave 6-pyrrolidin-1-yl-1H-indole as a white solid.
- 20
- f)     3-(6-Chloro-1-methyl-1H-indol-3-yl)-4-(6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2, 5-dione (1.2%) was prepared from 6-pyrrolidin-1-yl-1H-indole and 2-(6-chloro-1-methyl-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride.
- 25
- g)     3-(1-Methoxymethyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2, 5-dione was prepared from 1-methoxymethyl-6-pyrrolidin-1-yl-1H-indole and 2-(1-methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride.
- 30

- 5            1-Methoxymethyl-6-pyrrolidin-1-yl-1H-indole was prepared from 6-pyrrolidin-1-yl-1H-indole ( example 12 e) in the same manner as example 1(a) using chloromethyl methylether as the alkylating agent.
- 10           h)       3-(1-Methyl-6-nitro-1H-indol-3-yl)-4-(6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2, 5-dione: prepared by refluxing 3-(1-methoxymethyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2, 5-dione (above) in a mixture of acetic acid and aqueous HCl. After an aqueous work-up, the crude product was purified by silica gel chromatography.
- 15           i)       3-(1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-pyrrole-2,5-dione: prepared using 1-methyl-6-pyrrolidin-1-yl-1H-indole and 2-[1-(2,2-dimethylpropionyl)-1H-indol-3-yl]acetimidic acid isopropyl ester hydrochloride followed by deprotection using sodium methoxide in methanol.
- 20           j)       3-(1-Methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione (41mg, 13%) was prepared using 1-methyl-6-pyrrolidin-1-yl-1H-indole (150mg, 0.75 mmol) and 1-methyl-3-indoleacetimidic acid isopropyl ester hydrochloride (200mg, 0.75 mmol).
- 25           k)       3-(1-Methyl-1H-indol-3-yl)-4-[1-methyl-6-(4-methyl-piperazin-1-yl)-1H-indol-3-yl]pyrrole-2,5-dione (256 mg, 67%): prepared from 1-methyl-6-(4-methyl-piperazin-1-yl)-1H-indole (192 mg, 0.84 mmol), prepared as described in Example 11(a), and 1-methyl-3-indoleacetimidic acid isopropyl ester hydrochloride (224 mg, 0.84 mmol).
- 30           l)       3-(1-Methyl-1H-indol-3-yl)-4-(1-methyl-6-piperidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione (56 mg, 28%): prepared from 1-methyl-6-piperidin-1-yl-1H-indole (96 mg, 0.45 mmol) and 1-methyl-3-indoleacetimidic acid isopropyl ester hydrochloride (120 mg, 0.45 mmol).
- 35

- 5 m) 3-(6-Fluoro-1-methyl-1H-indol-3-yl)-4-(1-methoxymethyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione: prepared from 1-methoxymethyl-6-morpholin-4-yl-1H-indole and 2-(6-fluoro-1-methyl-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride.
- 10 n) 3-(6-Fluoro-1-methyl-1H-indol-3-yl)-4-(6-morpholin-4-yl-1H-indol-3-yl)-pyrrole-2,5-dione: prepared from 3-(6-fluoro-1-methyl-1H-indol-3-yl)-4-(1-methoxymethyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione by deprotection using hydrochloric acid in refluxing THF followed by refluxing in aqueous acetic acid.
- 15 o) 3-(1-Methyl-1H-indol-3-yl)-4-(6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione: prepared from 1-(4-methoxybenzyl)-6-morpholin-4-yl-1H-indole and 1-methyl-3-indoleacetimidic acid isopropyl ester hydrochloride followed by deprotection using sulfuric acid in trifluoroacetic acid.
- 20

### Example 13

#### **1-Methyl-3-[4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-1H-indole-6-carbonitrile**

- 25 a) 1-Methyl-6-morpholin-4-yl-1H-indole (3.89 g, 18 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (18 mL) and cooled at 0°C. Methyl chlorooxoacetate (2.4 mL, 26 mmol) was added to give a dark solution. Stirring was continued for 2 h at 0°C and more methyl chlorooxoacetate (0.40 mL, 4.3 mmol) was added. After a further 2 h, the solvent was evaporated. The resulting solid was taken up in ether, filtered and
- 30 washed well with ether to give crude methyl (1-methyl-6-morpholin-4-yl-1H-indol-3-yl)glyoxylate (6 g).
- b) Crude methyl (1-methyl-6-morpholin-4-yl-1H-indolyl-3)glyoxylate (6 g) in dioxane (300 mL) in a 500 mL round bottom flask was fitted with a reflux
- 35 condenser and a balloon on the top. The system was flushed with argon then

- 5 Pd/C (2 g, 10%) was added followed by sodium hypophosphite hydrate (20 g) in water (50mL). The mixture was heated under reflux for 5 h and more sodium hypophosphite hydrate (10 g) in water (10mL) was added. The mixture was refluxed for additional 3 h. and cooled. The solids were filtered off and washed well with EtOAc. The filtrate was washed with brine and dried (MgSO<sub>4</sub>).
- 10 Evaporation of the solvents and chromatography of the residue over silica gel using 20% EtOAc in hexanes gave (1-methyl-6-morpholin-4-yl-1H-indol-3-yl)acetic acid methyl ester (2.79 g, 54%).
- c) (1-Methyl-6-morpholin-4-yl-1H-indol-3-yl)-acetic acid methyl ester (2.67 g, 9.26 mmol) was suspended in concentrated NH<sub>4</sub>OH (20 mL) in a 100 mL flask, sealed and stirred for 24h. The mixture was transferred into a 500 mL flask and more NH<sub>4</sub>OH (80 mL) was added. The flask was again sealed and stirring was continued for another 24 h. The volatiles were removed under reduced pressure. (1-methyl-6-morpholin-4-yl-1H-indol-3-yl)acetamide (2.39g, 94%) was obtained after lyophilization.
- 20
- d) A solution of *t*-BuOK in THF (1 M, 18.9 mL, 18.9 mmol) was added dropwise to a mixture of methyl (6-cyano-1-methyl-1H-indol-3-yl)glyoxylate (1.85 g, 7.64 mmol) and (1-methyl-6-morpholin-4-yl-1H-indol-3-yl)-acetamide (1.74 g, 6.36 mmol) at 0°C. The cooling bath was removed after 15 min and the mixture was stirred at room temperature for 3 h. Concentrated hydrochloric acid (37%, 10 mL) was added and the reaction mixture was stirred for a further 30 min. The mixture was made basic with aqueous NaHCO<sub>3</sub> and extracted with CHCl<sub>3</sub> (3 x 500 mL). The combined organic extracts were washed with aqueous Na<sub>2</sub>CO<sub>3</sub> and dried (K<sub>2</sub>CO<sub>3</sub>). The extracts were filtered through a pad of silica gel, then evaporation of the solvents and crystallization of the crude product from acetone / EtOAc gave 1-methyl-3-[4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-1H-indole-6-carbonitrile (2.05 g, 69%).
- 25
- 30 Ref: Faul, M.M.; Winneroski, L.L.; Krumrich, C.A. *J. Org. Chem.* **1998**, *63*, 6053.
- 35



5

**Example 14**

In a manner similar to that described in Example 13, the following compounds were prepared. The starting materials were prepared in a manner analogous to that described in 13a), b), and c).

10

a) 3-(6-Methoxy-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione (103 mg, 23%): prepared from methyl (6-methoxy-1-methyl-1H-indol-3-yl)glyoxylate (257 mg, 1.04 mmol) and (1-methyl-6-morpholin-4-yl-1H-indol-3-yl)acetamide (259 mg, 0.95 mmol).

15

b) 3-(6-Fluoro-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione (72 mg, 42%): prepared from methyl (6-fluoro-1-methyl-1H-indol-3-yl)glyoxylate (95 mg, 0.40 mmol) and (1-methyl-6-morpholin-4-yl-1H-indol-3-yl)acetamide (100 mg, 0.37mmol).

20

c) 3-(6-Chloro-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione (96 mg, 83%): prepared from methyl(6-chloro-1-methyl-4-1H-indol-3-yl)glyoxylate (74 mg, 0.29 mmol) and (1-methyl-6-morpholin-4-yl-1H-indol-3-yl)-acetamide (67 mg, 0.245 mmol).

25

d) 3-(6-Bromo-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione (139 mg, 49%) was prepared from methyl (6-bromo-1-methyl-1H-indol-3-yl)glyoxylate (190 mg, 0.64 mmol) and (1-methyl-6-morpholin-4-yl-1H-indol-3-yl)acetamide (150 mg, 0.55 mmol).

30

e) 3-(1-Methyl-6-morpholin-4-yl-1H-indol-3-yl)-4-(1-methyl-6-trifluoromethyl-1H-indol-3-yl)pyrrole-2,5-dione (151 mg, 54%) was prepared from methyl (1-methyl-6-trifluoromethyl-1H-indol-3-yl)glyoxylate (172 mg, 0.60 mmol) and (1-methyl-6-morpholin-4-yl-1H-indol-3-yl)acetamide (150 mg, 0.55 mmol).

35

- 5 f) 3-(6-Bromo-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione (49 mg, 46%) was prepared from methyl (6-bromo-1-methyl-1H-indol-3-yl)-glyoxylate (68 mg, 0.23 mmol) and (1-methyl-6-pyrrolidin-4-yl-1H-indol-3-yl)acetamide (54 mg, 0.21 mmol).
- 10 g) 3-(6-Methoxy-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione (55 mg, 58%) was prepared from methyl (6-methoxy-1-methyl-1H-indol-3-yl)-glyoxylate (57mg, 0.23 mmol) and (1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-acetamide (54 mg, 0.21 mmol).
- 15 h) 3-(1-Methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-4-(1-methyl-6-trifluoromethyl-1H-indol-3-yl)pyrrole-2,5-dione (67 mg, 35%) was prepared from methyl (1-methyl-6-trifluoromethyl-1H-indol-3-yl)glyoxylate (111 mg, 0.39 mmol) and (1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)acetamide (100 mg, 0.39 mmol).
- 20 i) 3-(6-Chloro-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione (70 mg, 37%) was prepared from methyl (6-chloro-1-methyl-1H-indol-3-yl)glyoxylate (98 mg, 0.39 mmol) and (1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-acetamide (100 mg, 0.39 mmol).

25

**Example 15****1-Methyl-3-[4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-1H-indole-6-carbonitrile**

- 30 a) (1-Methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)acetic acid methyl ester (360 mg, 1.32 mmol) and NaOH (132 mg, 3.3 mmol) in methanol (8 mL) were heated at reflux for 30 min. The reaction mixture was cooled to 0°C and acidified using 1 N HCl. The mixture was extracted with EtOAc (3 x 100 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated.
- 35 Chromatography of the crude product over silica gel using 5-20% MeOH in

5 CH<sub>2</sub>Cl<sub>2</sub> gave (1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)acetic acid (241 mg, 71%).

(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-acetic acid methyl ester was prepared in a similar manner as described in examples 13 a) and b).

10

b) A solution of oxalyl chloride in CH<sub>2</sub>Cl<sub>2</sub> (2 M, 1.6 mL, 3.2 mmol) was added dropwise to a solution of 6-cyano-1-methyl-1H-indole (360 mg, 2.3 mmol) in ether (5 mL). Stirring was continued for 30 min at 0°C and the cooling bath was removed. After 2 h, more of the 2 M solution of oxalyl chloride (0.2 mL, 0.4 mmol.) was added. Stirring was continued at room temperature for additional 2h. The solid was filtered and washed with ether to give (6-cyano-1-methyl-1H-indol-3-yl)glyoxylyl chloride (450 mg, 79%).

15

Ref.: Troxler, F.; Hamisch, A.; Bormann, G.; Seemann, F.; Szabo, L.; *Helv. Chim. Acta*, 1968, 51(1), 1616.

20

c) 6-Cyano-1-methyl-1H-indolyl-3-glyoxylyl chloride (260 mg, 1.05 mmol) and (1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-acetic acid (241 mg, 0.93 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were stirred at 0°C. Triethylamine (0.41 mL, 2.95 mmol) was added and the mixture was stirred at room temperature for 16 h. The solvent was removed under vacuum and toluene (10 mL) and p-TsOH.H<sub>2</sub>O (0.35 g, 1.84 mmol) were added to the residue. After 2 h, methanol (5 mL) was added and stirring was continued until the presence of starting material could not be detected by TLC (40 % EtOAc/hexanes). The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with saturated Na<sub>2</sub>CO<sub>3</sub> (3x 50 mL). The aqueous layer was back extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 50 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated to give 0.30 g of a purple solid. Chromatography of the crude product over silica gel using 5% - 20% EtOAc / hexanes gave 1-methyl-3-[4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-furan-3-yl]-1H-indole-6-carbonitrile (0.19 g, 45 %) as a purple solid.

25

30

35

- 5 d) 1-Methyl-3-[4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-furan-3-yl]-1H-indole-6-carbonitrile (0.16 g, 0.36 mmol) was dissolved in dry DMF ( 5 mL , dried over 3 Å° molecular sieves) in a 50 mL round bottom flask. To this was added methanol (0.1 mL) and 1,1,1,3,3,3 hexamethyldisilazane (0.9 mL). The purple solution was stirred at room temperature overnight. Methanol  
10 (0.03 mL) and 1,1,1,3,3,3 hexamethyldisilazane (0.27 mL) were added and stirred for 3 h. The mixture was diluted with ethyl acetate (50 mL) and washed with brine. The aqueous layer was back extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were diluted with an equal volume of hexanes, dried (MgSO<sub>4</sub>), and passed over a pad of silica gel. The silica gel was washed  
15 with 1:1 ethyl acetate/hexanes (150 mL), and the filtrate was concentrated. Chromatography of the residue over silica gel using 25% - 40% EtOAc / hexanes gave 1-methyl-3-[4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-1H-indole-6-carbonitrile (71 mg, 44%) as a purple solid.

20 **Example 16**

3-(6-methoxymethyl-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione: prepared from 6-methoxymethyl-1-methyl-1H-indole and 1-methyl-6-morpholin-4-yl-1H-indole.

25 **Example 17**

3-[6-(2-Imidazol-1-yl-ethoxy)-1-methyl-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione

- a) A solution of n-butyllithium in hexane (1.6 M, 1.7 mL, 27.2 mmol) was added to  
30 6-bromo-1-methyl indole (5.0 g, 23.8 mmol) in dry THF (100 mL) at -78°C over 30 min. After 30 min, trimethylborate (2.93 g, 28.2 mmol) in dry THF (25 mL) was added. Stirring was continued at -78°C for 30 min. Methanol (12.5 mL) and water (12.5 mL) were added, and the mixture was stirred at room temperature for 3 h. It was diluted with ether (100 mL), and washed with sulfuric acid (1 N, 2  
35 x 100 mL) and water (2 x 100 mL). The aqueous layer was back extracted with

5 ether (2 x 100 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered over a pad of silica gel and the pad was washed with ether (100 mL). The filtrate was concentrated and the crude product was chromatographed over silica gel with 10 % to 25 % ethyl acetate / hexanes to give 1-methyl-1H-indol-6-yl-boronic acid (2.6 g, 62.5%).

10

b) 1-Methyl-1H-indol-6-yl-boronic acid (1.4 g, 8.0 mmol) was dissolved in ether (25mL). Hydrogen peroxide (15 %, 6 mL) was added over 5 minutes and the reaction mixture was stirred at room temperature for 1 h. The mixture was extracted with NaOH (1N, 2 x 50 mL) and the aqueous extracts were washed with ether (2x 50 mL). The aqueous layers were cooled to 0°C and acidified to pH 4.0 with 6 N HCl. The mixture was extracted with ether (3 x 100 mL) and the organic extracts were washed with water. The organic extracts were dried ( $\text{MgSO}_4$ ), filtered through a pad of silica gel and the pad was washed with ether (100 mL). After the filtrate was concentrated, the residue was chromatographed over silica gel with 10% to 20% ethyl acetate/ hexanes to give 1-methyl-1H-indol-6-ol as a yellow solid (0.56 g, 47 %).

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c) 1-Methyl-1H-indol-6-ol (0.36 g, 2.45 mmol), 1-(2-hydroxyethyl)imidazole (0.315 g, 2.82 mmol) and triphenylphosphine (0.767 g, 2.92 mmol) were dissolved in dry THF under argon at -78°C. Diethyl azodicarboxylate (0.47 mL, 2.95 mmol) was added over 2 min. The mixture was stirred at room temperature for 16 h. More triphenyl phosphine (0.7 g, 2.67 mmol) and DEAD (0.47 mL, 2.95 mmol) were added at -78°C. The reaction mixture was stirred for 24 h at room temperature then was diluted with ether (50 mL) and washed with water (2x 50 mL). The aqueous layer was back-extracted with ether (2 x 50 mL) and the combined organic extracts were dried ( $\text{MgSO}_4$ ) and evaporated. The crude red-orange oil was passed over a pad of silica gel and the pad was washed with 10% methanol/ methylene chloride (200 mL) to yield a maroon oil (3.15 g). Chromatography of the crude product over silica gel with 0-10% methanol/chloroform gave 6-(2-imidazol-1-yl-ethoxy)-1-methyl-1H-indole (0.19 g, 32%) as a thick brown oil.

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d) 6-(2-Imidazol-1-yl-ethoxy)-1-methyl-1H-indole (185 mg, 0.77 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) under argon at 0°C. To this was added oxalyl chloride (0.19 mL, 2.18 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). After stirring at 0°C for 4 h, the mixture was evaporated and dried under vacuum for 2 h. 2-(1-Methyl-6-nitro-1H-indol-3-yl)acetimidic acid isopropyl ester hydrochloride (239 mg, 0.77 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (3 mL) were added to the above green solid. Triethylamine (0.81 mL, 5.82 mmol) was added slowly at 0°C and the mixture was stirred at room temperature for 16 h. The mixture was evaporated to dryness and methanol (5 mL) and 12 N hydrochloric acid (1 mL) were added. The mixture was heated to 85°C for 1 h. After the solvents were evaporated, ethyl acetate (50 mL) was added and the mixture was carefully washed with 5% sodium bicarbonate (3 x 50 mL). The aqueous layer was back-extracted with ethyl acetate (2 x 50 mL), then the combined organic extracts were dried (MgSO<sub>4</sub>), filtered through a pad of silica gel and the pad was washed with 10 % methanol/CH<sub>2</sub>Cl<sub>2</sub> (400 mL). The filtrates were concentrated and the crude product was chromatographed on silica gel with 1% to 5% methanol/ ethyl acetate gave an orange solid. Further purification by dissolving the solid in hot CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and precipitating with ether (20 mL) yielded 3-[6-(2-imidazol-1-yl-ethoxy)-1-methyl-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione as an orange solid (0.103 g, 26 %).

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### Example 18

3-(1-Methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-pyrimidin-5-yl-1H-indol-3-yl)pyrrole-2,5-dione

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a) 1-methyl-1H-indol-6-yl-boronic acid (from example 17(b)) (0.86 g, 5 mmol) was suspended in dry dioxane (20 mL) and treated with 5-bromo-pyrimidine (1.0 g, 6.3 mmol), sodium carbonate (2.0 g), and tetrakis(triphenylphosphine)palladium (0) (120 mg, 0.10 mmol). The mixture was refluxed for 16 hr and cooled. This was diluted

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- 5 with hexane (20 ml), filtered through celite, and concentrated to dryness. The residue was purified by silica gel chromatography using ethyl acetate as solvent. 1-Methyl-6-pyrimidin-5-yl-1H-indole was crystallized from ether.
- b) 3-(1-Methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-pyrimidin-5-yl-1H-indol-3-yl)pyrrole-2,5-dione was prepared from 1-methyl-6-pyrimidin-5-yl-1H-indole and 2-  
 10 (1-methyl-6-nitro-1H-indol-3-yl)-acetimidic acid isopropyl ester hydrochloride.

### Example 19

- 3-(1-Methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrimidin-5-yl-1H-indol-3-yl)pyrrole-2,5-  
 15 dione: prepared from 1-methyl-6-pyrimidin-5-yl-1H-indole and 1-methyl-3-indole-acetimidic acid isopropyl ester hydrochloride as described in Example 18.

### Example 20

#### **CAPSULE FORMULATION**

Item	Ingredients	mg/Capsule				
		10 mg	50 mg	100 mg	250 mg	500 mg
1	Example 12d	10.0	50.0	100.0	250.0	500.0
2	Hydrous Lactose	154.0	114.0	148.0	42.0	82.0
3	Starch 1500	25.0	25.0	40.0	40.0	70.0
4	Talc	10.0	10.0	10.0	15.0	20.0
5	Magnesium Stearate	1.0	1.0	2.0	3.0	3.0
	<b>Total Fill Weight</b>	<b>200</b>	<b>200</b>	<b>300</b>	<b>350</b>	<b>675</b>

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#### Manufacturing Procedure:

1. Mix Items 1, 2 and 3 in a suitable mixer for 15 minutes.
2. Pass the mix from Step 1 through a Fitz mill using "00" screen at slow speed.
3. Add the adjusted amount of Items 4 and 5 and mix for 3 minutes in a suitable  
 25 mixer.
4. Fill the powder mix from Step 3 into a suitable size capsules.

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**Example 21**  
**TABLET FORMULATION**

Item	Ingredients	mg/Tablet					
		10 mg	50 mg	100 mg	400 mg	600 mg	1000 mg
KERNEL							
1	Example 12d	10.0	50.0	100.0	400.0	600.0	1000.0
2	Anhydrous Lactose	177.0	137.0	84.5	279.5	79.5	102.0
3	Croscarmellose Sodium	5.0	5.0	7.5	40.0	40.0	50.0
4	Povidone K 30	6.0	6.0	6.0	23.0	23.0	36.0
5	Magnesium Stearate	2.0	2.0	2.0	7.5	7.5	12.0
	Kernel Weight	200	200	200	750	750	1200
FILM COAT							
6	Hydroxypropyl Methylcellulose 6cps-2910	3.0	3.0	3.0	6.0	9.0	12.0
7	Talc	1.5	1.5	1.5	3.0	4.5	6.0
8	Titanium Dioxide	1.5	1.5	1.5	3.0	4.5	6.0
Total tablet weight		206	206	206	759	768	24.0

**Manufacturing Procedure:**

- 10 1. Mix Items 1, 2, 3 and 4 in a high shear mixer for 5 minutes.
2. Granulate the powder mix from Step 1 with purified water.
3. Dry the granulation from Step 2 at 50°C.
4. Pass the granulation from Step 3 through a suitable milling equipment.
5. Add the adjusted amount of Item 5 to the milled granulation from Step 4 and mix
- 15 for 5 minutes in a suitable mixer.
6. Compress the granulation from Step 5 on a suitable press.
7. Using a suitable air spray system, coat the kernels from Step 6 with a Film-Coat Suspension of Items 6, 7 and 8 in purified water to the desired weight.

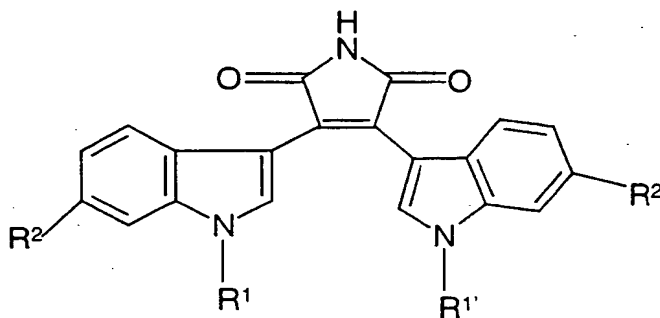


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CLAIMS

1. A compound of the formula

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wherein

R<sup>1</sup> and R<sup>1'</sup> are independently hydrogen or lower alkyl, lower alkenyl or lower alkynyl;

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R<sup>2</sup> is hydrogen, nitro, cyano, halogen, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy; and

R<sup>2'</sup> is a heteroaryl, heterocycle, ethyl substituted with a heteroaryl, or ethoxy substituted with a heteroaryl or heterocycle; or

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a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein R<sup>2'</sup> is a heteroaryl.

3. A compound of claim 2, wherein at least one of R<sup>1</sup> and R<sup>1'</sup> is lower alkyl.

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4. A compound of claim 3, wherein at least one of R<sup>1</sup> and R<sup>1'</sup> is methyl.

5. A compound of claim 4, wherein R<sup>2'</sup> is thiophenyl.

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6. A compound of claim 5, selected from the group consisting of

- 5 a) 3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-thiophen-2-yl-1H-indol-3-yl)pyrrole-2,5 dione;  
b) 3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-thiophen-3-yl-1H-indol-3-yl)pyrrole-2,5-dione;  
c) 3-(1-methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-thiophen-2-yl-1H-indol-3-yl)-pyrrole-2,5-dione; and  
10 d) 3-(1-methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-thiophen-3-yl-1H-indol-3-yl)pyrrole-2,5-dione.
7. A compound of claim 4, wherein R<sup>2'</sup> is furanyl.
- 15 8. A compound of claim 7, selected from the group consisting of  
a) 3-(6-furan-2-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)pyrrole-2,5-dione;  
b) 3-(6-furan-2-yl-1-methyl-1H-indol-3-yl)-4-(1H-indol-3-yl)pyrrole-2,5-dione;  
20 c) 3-(6-furan-2-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione.
9. A compound of claim 4, wherein R<sup>2'</sup> is imidazolyl which is unsubstituted or substituted with lower alkyl.
- 25 10. A compound of claim 9, selected from the group consisting of  
a) 3-[1-methyl-6-(1-methyl-1H-imidazol-2-yl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione;  
30 b) 3-(1-methyl-1H-indol-3-yl)-4-[1-methyl-6-(1-methyl-1H-imidazol-2-yl)-1H-indol-3-yl]-pyrrole-2,5-dione;  
c) 3-[1-methyl-6-(3-methyl-3H-imidazol-4-yl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione;  
d) 3-(1-methyl-1H-indol-3-yl)-4-[1-methyl-6-(3-methyl-3H-imidazol-4-yl)-1H-indol-3-yl]pyrrole-2,5-dione;  
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- 5 e) 3-(6-methoxy-1-methyl-1H-indol-3-yl)-4-[1-methyl-6-(3-methyl-3H-imidazol-4-yl)-1H-indol-3-yl]pyrrole-2,5-dione;
- f) 3-[6-(1-ethyl-1H-imidazol-2-yl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione;
- 10 g) 3-[6-(1H-imidazol-2-yl)-1-methyl-1H-indol-3-yl]-4-(1-methyl-1H-indol-3-yl)pyrrole-2,5-dione;
- h) 3-[6-(3H-imidazol-4-yl)-1-methyl-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione hydrochloride;
- i) 3-(6-imidazol-1-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)pyrrole-2,5-dione;
- 15 j) 3-(6-imidazol-1-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione;
- k) 3-(6-imidazol-1-yl-1-methyl-1H-indol-3-yl)-4-(6-methoxy-1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;
- l) 3-(6-bromo-1-methyl-1H-indol-3-yl)-4-(6-imidazol-1-yl-1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;
- 20 m) 3-[4-(6-imidazol-1-yl-1-methyl-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-1-methyl-1H-indole-6-carbonitrile;
- n) 3-[1-methyl-6-(2-methyl-imidazol-1-yl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione; and
- 25 o) 3-[6-(1H-imidazol-2-yl)-1-methyl-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2, 5-dione.
11. A compound of claim 4, wherein R<sup>2</sup> is thiazolyl.
- 30 12. A compound of claim 11, selected from the group consisting of
- a) 3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-thiazol-2-yl-1H-indol-3-yl)-pyrrole-2, 5-dione; and
- b) 3-(1-methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-thiazol-2-yl-1H-indol-3-yl)pyrrole-2,5-dione.
- 35

- 5           13.    A compound of claim 4, wherein R<sup>2'</sup> is pyrazolyl, which is unsubstituted or substituted with lower alkyl.
14.    A compound of claim 13, selected from the group consisting of
- 10           a)     3-(1-methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-pyrazol-1-yl-1H-indol-3-yl)pyrrole-2, 5-dione;
- b)     3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrazol-1-yl-1H-indol-3-yl)pyrrole-2, 5-dione;
- c)     3-(6-bromo-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrazol-1-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- 15           d)     3-[1-methyl-6-(2-methyl-2H-pyrazol-3-yl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione;
- e)     3-(1-methyl-1H-indol-3-yl)-4-[1-methyl-6-(2-methyl-2H-pyrazol-3-yl)-1H-indol-3-yl]pyrrole-2,5-dione;
- 20           f)     3-(6-bromo-1-methyl-1H-indol-3-yl)-4-[1-methyl-6-(2-methyl-2H-pyrazol-3-yl)-1H-indol-3-yl]pyrrole-2,5-dione.
15.    A compound of claim 4, wherein R<sup>2'</sup> is a pyrimidinyl.
16.    A compound of claim 15, selected from the group consisting of
- 25           a)     3-(1-methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-pyrimidin-5-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- b)     3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrimidin-5-yl-1H-indol-3-yl)pyrrole-2,5-dione.
17.    A compound of claim 4, wherein R<sup>2'</sup> is an isothiazolyl.
- 30           18.    A compound of claim 17, selected from the group consisting of
- a)     3-(6-isothiazol-5-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2, 5-dione;

- 5                   b)       3-(6-isothiazol-5-yl-1-methyl-1H-indol-3-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione.
19.       A compound of claim 1, wherein R<sup>2'</sup> is a heterocycle.
- 10       20.       A compound of claim 19, wherein at least one of R<sup>1</sup> and R<sup>1'</sup> is lower alkyl.
21.       A compound of claim 20, wherein at least one of R<sup>1</sup> and R<sup>1'</sup> is methyl.
- 15       22.       A compound of claim 21, wherein R<sup>2'</sup> is piperazine which is unsubstituted or substituted with lower alkyl, lower alkoxy or carbonyl.
23.       A compound of claim 22, wherein R<sup>2'</sup> is piperazine which is substituted with lower alkyl.
- 20       24.       A compound of claim 23, wherein R<sup>2'</sup> is 4-methyl-piperazinyl.
25.       A compound of claim 24, wherein the compound is 3-(1-methyl-1H-indol-3-yl)-4-[1-methyl-6-(4-methyl-piperazin-1-yl)-1H-indol-3-yl]pyrrole-2,5-dione.
- 25       26.       A compound of claim 21, wherein R<sup>2'</sup> is pyrrolidinyl.
27.       A compound of claim 26, selected from the group consisting of
- 30       a)       3-(1-methyl-6-nitro-1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- b)       3-(1-methyl-6-nitro-1H-indol-3-yl)-4-(6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2, 5-dione;
- c)       3-(6-fluoro-1-methyl-1H-indol-3-yl)-4-(6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2, 5-dione;

- 5 d) 3-(6-chloro-1-methyl-1H-indol-3-yl)-4-(6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2, 5-dione;
- e) 3-(1-methoxymethyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2, 5-dione;
- f) 3-(6-bromo-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- 10 g) 3-(6-methoxy-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- h) 3-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-4-(1-methyl-6-trifluoromethyl-1H-indol-3-yl)pyrrole-2,5-dione;
- i) 3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- 15 j) 1-methyl-3-[4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-1H-indole-6-carbonitrile;
- k) 3-(1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)-pyrrole-2,5-dione;
- 20 l) 3-(6-chloro-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-pyrrolidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione.

28. A compound of claim 21, wherein R<sup>2'</sup> is piperidinyl.

29. A compound of claim 28, wherein the compound is 3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-piperidin-1-yl-1H-indol-3-yl)pyrrole-2,5-dione.

30. A compound of claim 21, wherein R<sup>2'</sup> is morpholinyl.

31. A compound of claim 30, selected from the group consisting of

a) 3-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione;

b) 3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole 2,5-dione;

- 5 c) 1-methyl-3-[4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-1H-indole-6-carbonitrile;
- d) 3-(6-methoxy-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- 10 e) 3-(6-fluoro-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- f) 3-(6-chloro-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- g) 3-(6-bromo-1-methyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- 15 h) 3-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)-4-(1-methyl-6-trifluoromethyl-1H-indol-3-yl)pyrrole-2,5-dione;
- i) 3-(1,6-dimethyl-1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- j) 3-(1H-indol-3-yl)-4-(1-methyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- 20 k) 3-(6-fluoro-1-methyl-1H-indol-3-yl)-4-(1-methoxymethyl-6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- l) 3-(6-fluoro-1-methyl-1H-indol-3-yl)-4-(6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione;
- 25 m) 3-(1-methyl-1H-indol-3-yl)-4-(6-morpholin-4-yl-1H-indol-3-yl)pyrrole-2,5-dione.

32. A compound of claim 1, wherein R<sup>2</sup> is an ethoxy substituted by a heteroaryl or heterocycle.

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33. A compound of claim 33, wherein at least one of R<sup>1</sup> and R<sup>1'</sup> is lower alkyl.

34. A compound of claim 33, wherein at least one of R<sup>1</sup> and R<sup>1'</sup> is methyl.

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35. A compound of claim 35, wherein R<sup>2</sup> is ethoxy substituted by a heteroaryl.

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36. A compound of claim 36, wherein the heteroaryl is imidazolyl.

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37. A compound of claim 37, wherein the compound is 3-[6-(2-imidazol-1-yl-ethoxy)-1-methyl-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)pyrrole-2,5-dione.

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38. A pharmaceutical composition comprising as an active ingredient an effective amount of a compound of any one of claims 1-38 and a pharmaceutically acceptable carrier or excipient.

39. The pharmaceutical composition of claim 39 which is suitable for parenteral administration.

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40. The use of a compound as defined in any one of claims 1-38 for the preparation of medicaments for the treatment of cell proliferative disorders.

41. The use of compound as defined in any one of claims 1-38 for the preparation of medicaments for the treatment of cancer.

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42. A method for treating a cell proliferative disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 38.

43. The method of claim 43 wherein the cell proliferative disorder is cancer.

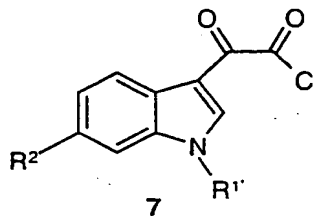
44. The method of claim 44 wherein the cancer is a solid tumor.

45. The method of claim 45 wherein the cancer is breast, colon or lung cancer.

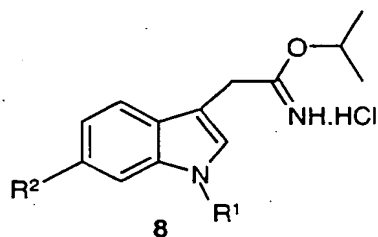
46. A process for the preparation of compounds of any of claims 1 to 38 comprising

d) reacting a compound of formula 7



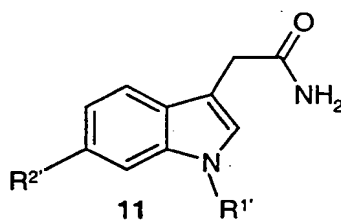


with a compound of formula 8

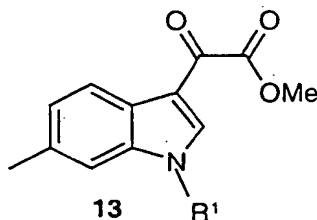


wherein  $R^{1'}$ ,  $R^{2'}$ ,  $R^1$  and  $R^2$  are as defined in claim 1;

e) reacting a compound of formula 11

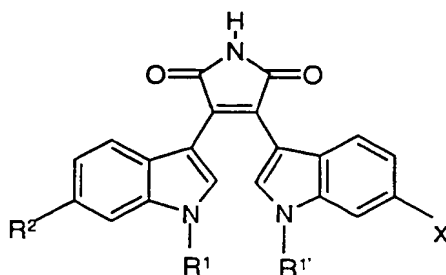


with a compound of formula 13



wherein  $R^{1'}$ ,  $R^{2'}$ , and  $R^1$  are as defined in claim 1, or

f) reacting a compound of formula 15



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wherein R<sup>1</sup>, R<sup>2</sup>, and R<sup>2'</sup> are as defined in claim 1 and X is Br or I,  
with a heteroaryl substituted trialkylstannane or boronic acid in the  
presence of a base catalyzed by a palladium catalyst;

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47. The novel compounds, novel pharmaceutical compositions, processes  
and methods as well as the use of such compounds substantially as  
described hereinbefore.